OL.
4
958

TETRAHEDRON

THE INTERNATIONAL JOURNAL OF ORGANIC CHEMISTRY

FOUNDED BY SIR ROBERT ROBINSON

HONORARY REGIONAL EDITORS

Prof. W. DOERING: 1901–A Yale Station, New Haven, Connecticut, U.S.A.
Prof. R. H. MARTIN: Laboratoire de Chimie Organique, Université Libre de Bruxelles, 50 Ave. F. D. Roosevelt, Brussels, Belgium.
Prof. A. N. NESMEYANOV: Akademiya Nauk SSSR, Bolshaya Kaluzhskaya 14, Moscow, U.S.S.R.
Prof. F. WEYGAND: Organisch-chemisches Institut, Technische Hochschule, München 2, Germany.

EXECUTIVE EDITOR

Prof. H. STEPHEN : 79 Hurst Rise Road, Cumnor Hill, Oxford, England.

HONORARY EDITORIAL ADVISORY BOARD

Europe

O. ACHMATOWICZ—Warsaw
K. BALENOVIĆ—Zagreb
D. H. R. BARTON—London
ENDRE BERNER—Oslo
J. W. CORNFORTH—London
C. DUFRAISSE—Paris
H. ERDTMAN—Stockholm
G. FODOR—Budapest
E. HAVINGA—Leiden
B. HELFERICH—Bonn
P. KARRER—Zurich
R. P. LINSTEAD—London
G. OURISSON—Strasbourg
V. PRELOG—Zurich
A. QUILICO—Milano
R. ROBINSON—London (Co-Chairman)
L. RUZICKA—Zurich
M. LORA-TAMAYO—Madrid
M. STACEY—Birmingham
A. TODD—Cambridge
W. TREIBS—Leipzig
STIG. VEIBEL—Copenhagen
F. WESSELY—Vienna
T. S. WHEELER—Dublin
O. WICHTERLE—Prague
G. WITTIG—Heidelberg

American Continent

P. D. BARTLETT—Cambridge, Mass.
H. C. BROWN—Lafayette
V. DEULOFEU—Buenos Aires
C. DJERASSI—Detroit
W. S. JOHNSON—Madison
L. MARION—Ottawa
J. D. ROBERTS—Pasadena
A. SANDOVAL—Mexico
K. WIESNER—New Brunswick
S. WINSTEIN—Los Angeles
R. B. WOODWARD—Cambridge, Mass. (Co-Chairman)

Far East

L. H. BRIGGS—Auckland
D. GINSBURG—Haifa
HUANG-MINLON—Shanghai
T. R. SESHADRI—Delhi
C. W. SHOPPEE—Sydney
S. SUGASAWA—Tokyo
K. VENKATARAMAN—Poona

Secretary to the Board of Editors: Dr. T. STEPHEN, 79 Hurst Rise Road, Cumnor Hill, Oxford.
Sub-editor: I. STUART, Journals Dept., Pergamon Press, 4 Fitzroy Square, London W.1.

VOLUME 4 1958

Copyright © Pergamon Press Ltd.

PERGAMON PRESS LTD.

LONDON NEW YORK PARIS LOS ANGELES

NOTES FOR CONTRIBUTORS

Submission of Original Contributions

Tetrahedron is intended to cover all aspects of organic chemistry, whether theoretical or practical, analytical or synthetic, physical or biological. Contributions may be in the form of papers, notes and preliminary communications. *Tetrahedron* publishes articles in English, French and German, but will arrange to have papers submitted in any other language translated by Pergamon Institute into English. They should be submitted for publication to the appropriate Honorary Regional Editor or, in cases of contributions emanating from areas not so covered, to the Executive Editor:

Professor William Doering (for the Western Hemisphere), 1901–A Yale Station, New Haven, Connecticut, U.S.A.

Professor R. H. Martin (contributions in the French Language), Laboratoires de Chimie Organique, Université Libre de Bruxelles, 50 Ave. F.D. Roosevelt, Brussels, Belgium.

Professor A. N. Nesmeyanov (for the U.S.S.R. and Eastern Europe), Akademiya Nauk SSSR, Bolshaya Kaluzhskaya 14, Moscow, U.S.S.R.

Professor H. Stephen, The Executive Editor, 79 Hurst Rise Road, Cumnor Hill, Oxford, England.

Professor Dr. F. Weygand (contributions in the German language), Organisch-chemisches Institut, Technische Hochschule, München 2, Germany.

Note: The contents of papers shall be the sole responsibility of the authors and publication shall not imply the concurrence of editors or publishers.

Form of Contributions

Manuscripts should be submitted in duplicate, double-spaced typescript. Contributions should be prepared in the form generally accepted for publication in the national journals. *Papers* should include an abstract in which the essential contents are briefly recapitulated. The abstract should be in the language of the paper, but for French or German papers an English version should also be provided. On the basis of originality, significance and breadth of interest to an international audience, *papers* are of the usual form reporting the result of original work. *Tetrahedron* offers an author the opportunity of including a longer review of his own published work, particularly if the paper represents the completion of a phase of a larger investigation.

Notes are a shorter form, useful for the suggestion of new interpretations or critical comment. *Preliminary Communications* are invited. An immediate decision on the acceptability of such contributions will be made by the receiving Editor, and publication in the next available issue is assured.

Preparation of Manuscript

Typographical correctness in the printed proofs is better assured by following the suggestions below in regard to mathematical expressions and other formulae.

Letters to be set in Greek type should be clearly indicated.

Confusion between the letter *l* and the numeral 1 when standing alone can be avoided by looping the letter *l* when typewritten. Similar differentiation between the O (or o) and zero 0 is advisable.

Subscripts and superscripts should be clearly indicated. Primes (as p') should be written or identified so that they will not be interpreted as the superior figure 1 (p^1).

In general, equations and formulae should be clearly and carefully written, taking care to have all figures and symbols, especially in fractions and equations, in the alignment in which they are to be printed. It would be helpful to have a third set of structural formulae attached.

Nomenclature following the I.U.P.A.C. Commission rules will always be accepted without modification. Otherwise the Editor's function in these matters will be advisory in nature.

Figures and illustrations should be separate from the typescript of the paper and should be clearly identified on the back by the author's name, the abbreviated title of the paper and the figure number. Legends should also be typed on a separate sheet. Line drawings which require re-drawing should include all relevant details and clear instructions for the draughtsman. If figures are already well drawn, it may be possible to reproduce them directly from the originals, or from good photoprints (preferably twice the size of the final published figure) if these can be provided. It is not possible to reproduce from prints with weak lines. Illustrations for reproductions should normally be about twice the final size required and the lettering and figures on them should be large enough to be clear when so reduced. Photographs should be included only where they are absolutely essential. The following standard symbols should be used on line drawings since they are easily available to the printers:

Tables should be so constructed as to be intelligible without reference to the text. Every table and column should be provided with an explanatory heading. Units of measure must always be clearly indicated. The same data should not be reproduced in both tables and figures.

References and footnotes shall be numbered consecutively in the text and shall be inserted immediately following their first introduction. Full references should be given as numbered footnotes, containing the names of all the authors, preceded by initials, title of journal (preferably abbreviated in accordance with current *Tetrahedron* practice), volume number, first page number and year, in the following way:

[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith and D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

Abbreviations are used freely in *Tetrahedron*, particularly in setting the experimental section. For the most part these are not followed by a full stop (period). Among the more commonly used abbreviations, these may be listed:

g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (liter), in. (inch) but in^2

New compounds should be indicated by underlining the name (for italics) at its first mention (including headings) in the experimental section only, and by giving analytical results in the form: (Found: C, 62·9; H, 5·4. $C_{18}H_{12}O_4N$ requires C, 63·2; H 5·3%).

Analytical results for compounds which have previously been adequately described in the literature should be given in the form: (Found: C, 62·9; H, 5·4. Calc. for $C_{18}H_{12}O_4N$: C, 63·2; H, 5·3%). The punctuation should be noted.

Proofs and Reprints

Proofs will be sent to authors for correction when their contribution is first set, but there is rarely time for page proofs also to be sent for checking. This will be done, however, where the amount of alteration makes it advisable. Proofs of text, and illustrations which cannot be set in type, will not be received simultaneously. Twenty-five free *reprints* (without covers) of papers having one author will be provided. Where there is more than one author, each additional author will receive 10 free reprints. Additional copies can be obtained if ordered when proofs are returned. A reprint order form will accompany first proofs.

LIST OF CONTENTS

VOLUME 4

NUMBERS 1/2

G. Chiurdoglu et J. Decot: Contribution à l'étude des composes sequiterpéniques—II. Étude de la structure du bi*cyclo*vétivénol et du tri*cyclo*vétivénol, alcools primaires de l'essence de vetiver . . 1
M. Lora-Tamayo: Some results obtained in the utilisation of quinones as philodiene . . . 17
C. R. Patrick: Some aspects of the thermochemistry and thermodynamics of fluorocarbons . . 26
I. Chmielewska, J. Cieślak, K. Gorczyńska, B. Kontnik et K. Pitakowska: Structure de la yangonine étude spectrographique dans l'ultraviolet et l'infrarouge 36
M. L. Scarpati and G. Oriente: Chicoric acid (dicaffeyltartic acid): its isolation from chicory (*Chicorium intybus*) and synthesis 43
A. Siegel, F. Wessely, P. Stockhammer, F. Antony und P. Klezl: Über die Einwirkung von Alkalihydroxydlösungen auf *o*-Chinolacetate 49
Takashi Kubota: Volatile constituents of black-rotted sweet potato and related substances . . 68
K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis: Annotinine—II. The complete structure 87
P. K. Grover and T. R. Seshadri: Preparation and constitution of *iso*pinastric acid . . . 105
Hugh M. Smith, John M. Smith and F. S. Spring: The triterpenoids—LVI. The chemistry of the soyaspagogenols A, B and C 111
S. E. Flores, J. Herrán and H. Menchaca: The synthesis of penduletin 132
I. Chmielewska and J. Cieślak: Vitamins and antivitamins K: tautomerism of dicoumarol . . 135
C. A. Barson and J. C. Bevington: A tracer study of the benzoyloxy radical 147
F. Sparatore, R. Greenhalgh and Leo Marion: A suggested structure for delsoline . . . 157
B. C. Saunders and B. P. Stark: Studies in peroxidase action—XII. Transiodination and related processes 169
W. von E. Doering, M. Saunders, H. G. Boynton, H. W. Earhart, E. F. Wadley, W. R. Edwards and G. Laber: The 1,1,2,3,4,5,6-heptamethylbenzenonium iron 178
V. M. Micović and Miss A. Stojiljković: The condensations of polyhydric alcohols and monosaccharides with *cyclo*pentanone and *cyclo*hexanone 186
Notes:
B. C. Saunders and B. P. Stark: Esters containing phosphorus—XVI. A new colour reaction for the detection and estimation of dialkyl phosphites 197
B. C. Saunders and B. P. Stark: Esters containing phosphorus—XVII. Detection and estimation of dialkyl phosphites in the presence of trialkyl phosphites 198
Preliminary Communication:
Hayao Nawa, Masao Uchibayashi, Rokuro Takeda, Itaru Nakanishi, Tsunaharu Kusaka, Jiro Terumichi, Minoru Uchida, Michio Katsumata, Kikuko Yoshino and Hiroshi Fujitani: Transformation of steroids by Pseudomonas 201
Papers to be published in future issues 203
Errata 204

NUMBERS 3/4

Shigehiko Sugasawa and Ryuji Tachikawa: Extension of Bischler-Napieralski reaction—I. Synthesis of *iso*quinoline derivatives: a synthesis of *rac.*-apomorphine dimethyl ether . . . 205
Erling Bernatek: Ozonolysis of naphthoquinones—I. Ozonolysis of 1:4-naphthoquinone in chloroform 213
R. P. Evstigneeva and N. A. Preobrazhensky: Synthesis of ipecacuanha alkaloids 223
L. Velluz, B. Goffinet et G. Amiard: Sur le comportement photochimique des 19-nor $\Delta^{5,7}$-stéroides 241
V. Herout and V. Sýkora: The chemistry of cadinenes and cadinols 246
R. Aneja, S. K. Mukerjee and T. R. Seshadri: A study of the origin and modifications of the C_5 unit in plant products—New synthesis of angelicin and psoralen 256
V. K. Ahluwalia, A. C. Mehta and T. R. Seshadri: Constitution of dalbergin—IV. A novel transformation of O-methyldalbergin 271
M. G. Rossmann and W. N. Lipscomb: The sesquiterpenoid iresin 275
P. Narasimha Rao and K. Raman: A stereospecific synthesis of (±)-ferruginol 294
J. N. T. Gilbert and David W. Mathieson: Cucurbitacin E: some preliminary observations . 302
T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai: Chemical examination of *Tylophora asthmatica*—II 311
J. F. Ford, R. C. Pitkethly and V. O. Young: Stereochemistry of the co-oxidation products of indene and thiophenol 325

KUNIO SUKIGARA, YOSHITERU HATA, YUKIO KURITA and MASAJI KUBO: The dipole moments and the structures of chloro- and bromo-crotonolactones 337
BENJAMIN FRYDMAN, RENATE BENDISCH and VENANCIO DEULOFEU: A synthesis of laudanine and (±)-pseudocodamine: resolution into the optical isomers 342
J. S. BRIMACOMBE, A. B. FOSTER, M. STACEY and D. H. WHIFFEN: Aspects of stereochemistry—I. Properties and reactions of some diols 351
C. ENZELL and H. ERDTMAN: The chemistry of the natural order cupressales—XXI. Cuparene and cuparenic acid, two sesquiterpenic compounds with a new carbon skeleton 361
CARL DJERASSI, O. HALPERN, D. I. WILKINSON and E. J. EISENBRAUN: Macrolide antibiotics—VIII. The absolute configuration of certain centers in neomethymycin, erythromycin and related antibiotics 369
E. C. KOOYMAN and G. C. VEGTER: Bicyclanes—I. The halogenation of 2:2:1-bi*cyclo*heptane (norbornane) 382
G. BERTI: Stereochemistry of the halolactonisation reaction. The reaction of *cis*- and *trans*-stilbene-2-carboxylic acids with halogens 393
A. BURAWOY, J. P. CRITCHLEY and A. R. THOMPSON: Electronic spectra of organic molecules and their interpretation—IV. Effect of terminal atoms with lone electron pairs on the K-bands of conjugated systems 403
Notes:
K. WIESNER, F. BICKELHAUPT and Z. VALENTA: The structure and substitution of the C–D ring system of delphinine 418
G. V. BHIDE, N. R. PAI, N. L. TIKOTKAR and B. D. TILAK: Synthesis of 3-desoxy-B-nor-6-aza-D-homoequilenin 420
D. F. C. MORRIS: The hydration heat of the benzenesulphonate ion 423
M. W. WHITEHOUSE and P. W. KENT: Synthesis of methyl 2-acetamido-2-deoxy-β-D-glucofuranoside 425
Book Reviews:
" 'AnalaR' Standards for Laboratory Chemicals" (reviewed by S. P. DATTA) 430
H. v. EULER und B. EISTERT: "Chemie und Biochemie der Reduktone und Reduktonate" (reviewed by G. HESSE) 430
W. KLYNE and P. B. D. DE LA MARE (Editors): "Progress in Stereochemistry" (reviewed by S. P. DATTA) 431
Papers to be published in future issues 432

AUTHOR INDEX

(B) denotes Book Review

AHLUWALIA, V. K. p. 271
ANEJA, R. p. 256
ANTONY, F. p. 49
AMIARD, G. p. 241
AYER, W. A. p. 87
BARSON, C. A. p. 147
BENDISCH, RENATE p. 342
BERNATEK, ERLING p. 213
BERTI, G. p. 393
BEVINGTON, J. C. p. 147
BHIDE, G. V. p. 420
BICKELHAUPT, F. p. 418
BOYNTON, H. G. p. 178
BRIMACOMBE, J. S. p. 351
BURAWOY, A. p. 403
CHIURDOGLU, G. p. 1
CHMIELEWSKA, I. pp. 36, 135
CIESLAK, J. pp. 36, 135
CRITCHLEY, J. P. p. 403
DATTA, S. P. pp. 430(B), 431(B)
DECOT, J. p. 1
DEULOFEU, VENANCIO p. 342
DJERASSI, CARL p. 369
DOERING, W. VON E. p. 178
EARHART, H. W. p. 178
EDWARDS, W. R. p. 178
EISENBRAUN, E. J. p. 369
ENZELL, C. p. 361
ERDTMAN, H. p. 361
EVSTIGNEEVA, R. P. p. 223
FLORES, S. E. p. 132
FORD, J. F. p. 325
FOSTER, A. B. p. 351
FOWLER, L. R. p. 87
FRANCIS, J. E. p. 87
FRYDMAN, BENJAMIN p. 342
FUHTANI, HIROSHI p. 201
GILBERT, J. N. T. p. 302
GOFFINET, B. p. 241
GORCZYNSKA, K. p. 36
GOVINDACHARI, T. R. p. 311
GREENHALGH, R. p. 157
GROVER, P. K. p. 105
HALPERN, O. p. 369
HATA, YOSHITERU p. 337
HEROUT, V. p. 246
HERRÁN, J. p. 132
HESSE, G. p. 430(B)
KATSUMATA, MICHIO p. 201
KENT, P. W. p. 425
KLEZL, P. p. 49
KONTNIK, B. p. 36
KOOYMAN, E. C. p. 382
KUBO, MASAJI p. 337
KUBOTA, TAKASHI p. 68
KURITA, YOKIO p. 337
KUSAKA, TSUNAHARU p. 201
LABER, G. p. 178
LAKSHMIKANTHAM, M. V. p. 311
LIPSCOMB, W. N. p. 275
LORA-TAMAYO, M. p. 17
MARION, LEO p. 157
MATHIESON, DAVID W. p. 302
MEHTA, A. C. p. 271
MENCHACA, H. p. 132
MICOVIC, V. M. p. 186
MORRIS, D. F. C. p. 423
MUKERJEE, S. K. p. 256
NAGARAJAN, K. p. 311
NAKANISHI, ITARU p. 201
NARASIMHA RAO, P. p. 294
NAWA, HAYAO p. 201
ORIENTE, G. p. 43
PAI, B. R. p. 311
PAI, N. R. p. 420
PATRICK, C. R. p. 26
PITAKOWSKA, K. p. 36
PITKETHLY, R. C. p. 325
PREOBRAZHENSKY, N. A. p. 223
RAMAN, K. p. 294
ROSSMANN, M. G. p. 275
SAUNDERS, B. C. pp. 169, 197, 198
SAUNDERS, M. p. 178
SCARPATI, M. L. p. 43
SESHADRI, T. R. pp. 105, 256, 271
SIEGEL, A. p. 49
SMITH, HUGH M. p. 111
SMITH, JOHN M. p. 111
SPARATORE, F. p. 157
SPRING, F. S. p. 111
STACEY, M. p. 351
STARK, B. P. pp. 169, 197, 198
STOCKHAMMER, P. p. 49
STOJILJKOVIC, A. (Miss) p. 186
SUGASAWA, SHIGEHIKO p. 205
SUKIGARA, KUNIO p. 337
SYKORA, V. p. 246
TACHIKAWA, RYUJI p. 205
TAKEDA, ROKURO p. 201
TERUMICHI, JIRO p. 201
THOMPSON, A. R. p. 403
TIKOTKAR, N. L. p. 420
TILAK, B. D. p. 420
UCHIBAYASHI, MASAO p. 201
UCHIDA, MINORU p. 201
VALENTA, Z. pp. 87, 418
VEGTER, G. C. p. 382
VELLUZ, L. p. 241
WADLEY, E. F. p. 178
WESSELY, F. p. 49
WHIFFEN, D. H. p. 351
WHITEHOUSE, M. W. p. 425
WIESNER, K. pp. 87, 418
WILKINSON, D. I. p. 369
YOSHINO, KIKUKO p. 201
YOUNG, V. O. p. 325

VOL. 4 1958

OL.
4
958

VOL.
4
1958

Tetrahedron, 1958, Vol. 4, pp. 1–16. Pergamon Press Ltd., London

CONTRIBUTION A L'ÉTUDE DES COMPOSÉS SESQUITERPÉNIQUES—II

ÉTUDE DE LA STRUCTURE DU BI*CYCLO*VÉTIVÉNOL ET DU TRI*CYCLO*VETIVÉNOL, ALCOOLS PRIMAIRES DE L'ESSENCE DE VETIVER*

G. CHIURDOGLU et J. DECOT
Université Libre de Bruxelles (Belgique). Faculté des Sciences, Service de Chime Générale II

(*Received* 20 *July* 1957)

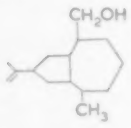
Résumé—Les structures du bi*cyclo*vétivénol (I) et du tri*cyclo*vétivénol (II), alcools primaires de l'essence de vetiver séparés précédemment par Ruzicka et par Semmler, ont été déterminées conjoinement par des méthodes chimiques classiques et par spectroscopie infra-rouge, au niveau des hydrocarbures éthyléniques provenant de la pyrolyse des acétates des dihydroalcools correspondants: le bi*cyclo*vétivéne (III) et le tri*cyclo*vétivéne (IV).

Les structures de ces alcools sont celles des: 6-hydroxyméthyl-2-méthyl-9-*iso*propényl-(0,3,5)-bi*cyclo*décane (I) et 2-hydroxyméthyl-9-*iso*propényl-3,6,endométhylène-(0,3,5)-bi*cyclo*décane (II).

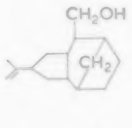
Abstract—The structures of bi*cyclo*vetivenol (I) and tri*cyclo*vetivenol (II), two primary alcohols isolated earlier by Ruzicka and Semmler, have been determined using classical chemical methods and infra-red spectroscopy.

The determinations are based on the study of the corresponding unsaturated hydrocarbons bi*cyclo*vetivene (III) and tri*cyclo*vetivene (IV), obtained by pyrolysis of the acetates of the corresponding dihydroalcohols.

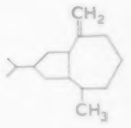
The structures of the alcohols are, respectively: 6-hydroxymethyl-2-methyl-9-*iso*propenyl-(0:3:5)-bi*cyclo*decane (I) and 2-hydroxymethyl-9-*iso*propenyl-3:6-endomethylene-(0:3:5)-bi*cyclo*-decane (II).



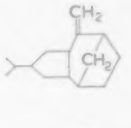
I



II



III



IV

L'HUILE de vetiver, signalée pour la première fois en 1901,[1] est très riche en substances sesquiterpéniques. Elle comprend, outre des cétones (α- et β-vétivones) et un hydrocarbure tricyclique $C_{15}H_{24}$, dont les structures ont été établies respectivement par Pfau et Plattner[2,3] et par Chiurdoglu et Tullen[4], des alcools dont les structures sont restées indéterminées. Parmi ces derniers, il existe deux alcools primaires. L'un, $C_{15}H_{26}O$, est bicyclique, l'autre, $C_{15}H_{24}O$, est tricyclique. Nous les appellerons respectivement *bicyclovétivénol primaire* (I) et *tricyclovétivénol primaire* (II). Semmler[5]

*Communication précédente[4]

[1] E. Theulier, *Bull. Soc. Chim. Fr.* **25**, 454 (1901).
[2] A. S. Pfau et P. A. Plattner, *Helv. Chim. Acta* **22**, 640 (1934).
[3] A. S. Pfau et P. A. Plattner, *Helv. Chim. Acta* **23**, 768 (1940).
[4] G. Chiurdoglu et P. Tullen, *Bull. Soc. Chim. Belg.* **66**, 169 (1957).
[5] F. W. Semmler, F. Risse et F. Schröter, *Ber. Dtsch. Chem. Ges.* **45**, 2347 (1912).

et Ruzicka[6] ont isolé des échantillons de ces alcools au départ d'huiles de Java et de La Réunion et en ont décrit les constantes physiques. Ruzicka a, de plus, signalé la formation de l'eudalène et du cadalène par déshydrogénation sur soufre du bi*cyclo*vétivénol.

L'objet de ce travail était d'étudier les structures du bi*cyclo*vétivénol (I) et du tri*cyclo*vétivénol (II). En fait, étant donné les difficultés d'isolement de chacun d'eux—l'essence de vetiver renferme également des alcools tertiaires*—nous avons préféré réaliser cette étude au niveau des hydrocarbures éthyléniques correspondants. Convenablement formés, ceux-ci sont en effet faciles à séparer.

I. OBTENTION ET SÉPARATION DU BI*CYCLO*VÉTIVÈNE (III) ET DU TRI*CYCLO*VÉTIVÈNE (IV). APPROCHES STRUCTURALES

*1. Séparation du mélange de bi*cyclo*vétivénol et de tri*cyclo*vétivénol par acétylation*

L'essence de départ provient du Congo Belge. Elle contient 45% d'alcools primaires. Les constantes physiques de cette essence sont: $d^{20/4}$: 1,001; n_D^{20}: 1,525; $[\alpha]_D^{20}$: +24°3.

L'essence de vetiver, neutralisée et débarrassée de l'hydrocarbure qu'elle renferme (6%), est traitée par l'anhydride acétique. Après estérification des alcools primaires, on élimine l'excès d'anhydride en même temps que les hydrocarbures formés par déshydratation des alcools tertiaires.

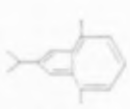
Le mélange des acétates (V/VI) de bi*cyclo*vétivénol (I) et de tri*cyclo*vétivénol (II) est percolé sur silice activée puis rectifié par distillation. Le mélange accuse, alors, les valeurs des constantes physiques ci-après:
$Eb_{0,4}$: 106°–111°; $d^{20/4}$: 1,0159; n_D^{20}: 1,5050. Son spectre confirme la présence de deux alcools: ν_{C-O}: 1033 et 1038 cm^{-1}; ν_{C-C}: 1637 et 1642 cm^{-1}.

Déshydrogénation. La pyrolyse du mélange des acétates (V/VI) de bi*cyclo*vétivénol et de tri*cyclo*vétivénol, à 500°, suivie de la déshydrogénation des diéniques formés ($Eb_{0,2}$: 66–69°; $d^{20/4}$: 0,9343; n_D^{20}: 1,5325) sur sélénium, à 280–300°, fournit le *vétivazulène* (VII) (trinitrobenzénate: $F = 147°5$, épreuve de mélange sans dépression) ainsi que l'*eudalène* (VIII) (8%) (picrate: $F = 89$–$89°5$, épreuve de mélange sans dépression, spectre infra-rouge identique à celui de Sorm.[7] Nous n'avons pas décelé de vétivalène (IX)† dans le déshydrogénat obtenu.

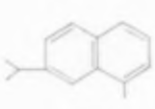
Double liaison. La détermination de la double liaison, par microhydrogénation,[8] dans le mélange des acétates (V/VI) montre qu'elle est unique. L'examen infra-rouge

* Ceux-ci font l'objet d'un travail en cours.

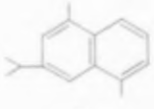
† Pfau et Plattner sont montré que la déshydrogénation des hydrocarbures dérivant des vétivones conduit au vétivazulène (VII) et à l'eudalène (VIII). Toutefois, une petite quantité de vétivalène (IX) peut également se former.



VII



VIII



IX

[6] L. Ruzicka, E. Capato et H. Huyser, *Rec. Trav. Chim.* **47**, 370 (1928).
[7] J. Pliva, V. Herout, B. Schneider et F. Sorm, *Coll. Czech. Com.* **18**, 500 (1953).
[8] G. Chiurdoglu, *Bull. Soc. Chim. Belg.* **50**, 31 (1941).

révèle que cette double liaison est du type $\diagdown C{=}CH_2$ ($\delta = 890$ cm^{-1}, $2\delta = 1780$ cm^{-1}) et peut, dès lors, être soit semicyclique: méthylénique, soit exocyclique: *iso*propénylique. Le fait qu'elle se transpose aisément au cours de diverses manipulations, telle la distillation, pour donner, entre autre, une double liaison biquaternaire, nous a conduit à admettre que l'on est en présence d'un groupe *iso*propénylique.

2. *Bi*cyclo*vétivène* (III) *et tri*cyclo*vétivène* (IV)

Par hydrogénation sur Ni–Ra, on passe du mélange des acétates V/VI de bi*cyclo*vétivénol et de tri*cyclo*vétivénol à celui de dihydrobi*cyclo*vétivénol et de dihydrotri*cyclo*vétivénol: $Eb_{0,2} = 105$–$111°$ $n_D^{20} = 1{,}5050$; $d^{20/4} = 0{,}9290$; deux bandes ν_{C-O}: 1033 et 1038 cm^{-1}). L'hydrogénation du mélange des acétates V/VI est quantitative, ce qui confirme la présence d'une seule double liaison dans chacun des alcools.

Le mélange des acétates V/VI est pyrolysé a 500–550°, sous azote, et l'on obtient, avec un bon rendement, le mélange de bi*cyclo*vétivène (III) et de tri*cyclo*vétivène (IV):

$$Eb_{0,1} = 53\text{–}59°;\ d^{20/4} = 0{,}9275;\ n_D^{20} = 1{,}5800$$

La distillation fractionnée de ce mélange de *cyclo*oléfines au moyen d'une colonne Todd de vingt plateaux théoriques permet la séparation, après quatre tours, de deux fractions de tête représentant environ 65% du distillat. Ces fractions accusent une valeur de RM_D proche de 64,45 et contiennent, par conséquent, l'oléfine dérivant du dihydrotri*cyclo*vétivénol: le tri*cyclo*vétivène (IV). La fraction de queue de la distillation présente une valeur de $RM_D = 66{,}67$. Elle est composée, dès lors, de bi*cyclo*vétivène (III), hydrocarbure de déshydratation du dihydrobi*cyclo*vétivénol.

3. *Hypothèse de travail*

Les résultats fragmentaires obtenus permettent, d'ores et déjà, d'élaborer des hypothèses de travail: le bi*cyclo*vétivénol (I) et le tri*cyclo*vétivénol (II) posséderaient, l'un et l'autre, une structure vétivazulénique puisque la déshydrogénation de ces alcools engendre du vétivazulène et de l'eudalène.

Chez ces alcools, la double liaison serait localisée sur le groupe *iso*propényle.

Enfin, le bi*cyclo*vétivène (III) et le tri*cyclo*vétivène (IV) provenant de la pyrolyse des acétates des dihydroalcools présentent, nécessairement, le groupe méthylène, doublement lié au cycle, à l'endroit où se trouve, dans les alcools de départ, le chainon —CH_2OH.

II. ETUDE STRUCTURALE DU BI*CYCLO*VÉTIVÈNE (III). STRUCTURE DU BICYCLOVÉTIVÉNOL (I)

1. *Constantes du bi*cyclo*vétivène* (III)

Cette *cyclo*oléfine formée a partir du dihydrobi*cyclo*vétivénol et isolée comme nous l'avons indique plus haut, présente les valeurs des constantes physiques suivantes:

$$Eb_{2,5} = 112°5\text{–}113°;\ d^{20/4} = 0{,}9170;\ n_D^{20} = 1{,}5046;\ RM_D = 66{,}59$$

(calculé pour $C_{15}H_{26}$, 1/$^-$: 66,67); $[\alpha]_D^{20} = +22°70$.

Analyse: trouvé: C = 87,45, H, = 12,60 (calculé: C = 87,29, H = 12,71).

La mesure de l'indice de non saturation par microhydrogénation[8] indique une seule double liaison. Pour $a = 100$ mg, V_{H_2} obs. = 11,04 ml (calculé: 10,88).

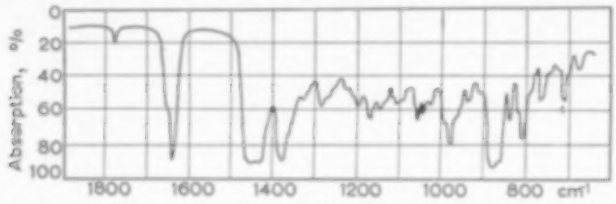


FIG. 1. Spectre infra-rouge du bi*cyclo*vétivène (III). (Spectrographe double faisceau, cellule 0,080 mm.)

2. *Déshydrogénation du bi*cyclo*vétivène*

Traité par du sélénium, durant deux heures à 280–300°, le bi*cyclo*vétivène fournit un déshydrogénat composé de vétivazulène (14%) et d'un naphtalénique (4%). Le vétivazulène a été identifié par l'intermédiaire de son trinitrobenzénate: $F = 150°$, épreuve de mélange concluante. Le naphtalénique donne un picrate $F = 90$–$90°5$ accusant à l'épreuve de mélange avec le picrate de l'eudalène de référence ($F = 92°$) une dépression de 15°. L'analyse infra-rouge du naphtalénique (Fig. 2) montre

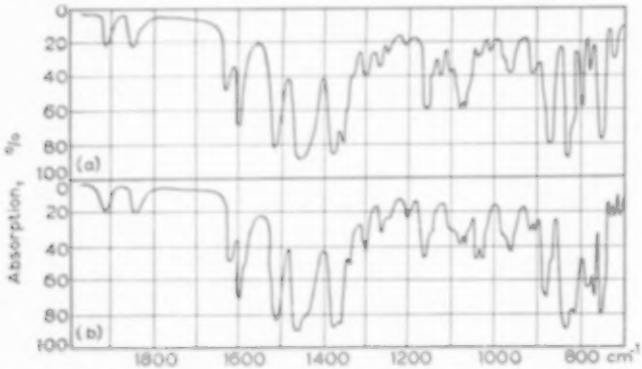


FIG. 2. Spectre I.R. du naphtalénique obtenu par déshydrogénation de III (courbe *a*; double beam; cell. 0,025 mm) et de l'eudalène, d'après Sorm[7] (courbe *b*; cell. 0,050 mm).

toutefois, sans ambiguïté, qu'il s'agit d'eudalène (VIII) souillé d'un deuxième naphtalénique, probablement le vétivalène (IX) représenté, en particulier, par une bande assez forte en 785 cm^{-1}.

3. *Emplacement du groupe hydroxyméthyle dans le* bicyclo*vétivénol. Ozonolyse du bi*cyclo*vétivène*

La pyrolyse de l'acétate du dihydrobi*cyclo*vétivénol en bi*cyclo*vétivène (III) introduit, en lieu et place du groupe hydroxyméthyle, le chaînon méthylène: bandes fortes en 1639 et 890 cm^{-1}, harmonique en 1780 cm^{-1}.

En fait, l'analyse conjointe I.R. et Raman indique, en outre, la présence de l'isomère à double liaison biquaternaire, formé par transposition du premier.

L'analyse quantitative du produit brut de pyrolyse montre qu'il est composé de 67% de la forme semicyclique III et de 33% de la forme endocyclique III'.

La fraction des produits neutres de l'ozonolyse présente les nombres d'onde

suivants: 1706, 1718 et 1742 cm^{-1}. Un traitement à l'hypobromite fait disparaître la seconde fréquence. La dernière se retrouve en solution acide. L'attribution des bandes est, dès lors, la suivante: 1706 cm^{-1} représente une *cyclo*heptanone, 1744 cm^{-1} une *cyclo*pentanone et 1718 cm^{-1} une méthylalcoylcétone.

4. *Bi*cyclo*vétivane* (X)

Le bi*cyclo*vétivène (III) a été transformé en bi*cyclo*vétivane (X) par hydrogénation sur Ni–Ra, à 100° et sous 50 atmosphères. Analyse: trouvé: C = 86,25, H = 13,77; calculé pour $C_{15}H_{28}$: C = 86,45, H = 13,55.

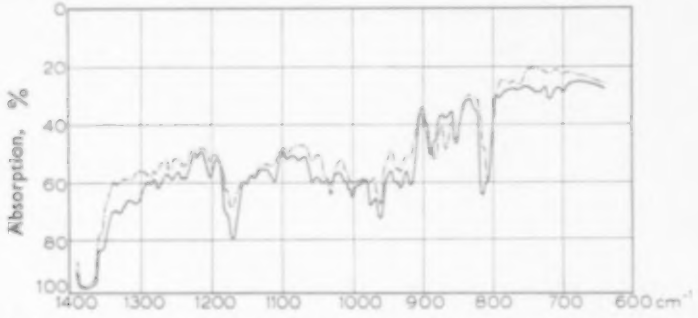


FIG. 3. Application du procédé de Sorm. Spectres du bi*cyclo*vétivane (X) (trait plein) et du 2,6-diméthyl-9-*iso*propyl-(0,3,5)-bi*cyclo*décane (en pointillé) (Spectrographe double faisceau, cell. 0,10 mm.)

L'application du procédé de Sorm[9] montre qu'il y a identité entre le bi*cyclo*vétivane et le 2,6-diméthyl-9-*iso*propyl-(0,3,5)-bi*cyclo*décane* (Fig. 3) préparés, tous deux, dans les mêmes conditions. Le tableau 1 contient les valeurs des constantes physiques de notre échantillon de bi*cyclo*vétivane. A leurs côtés, nous avons indiqué les valeurs signalées par Naves et Perrottet[10] pour le 2,6-diméthyl-9-*iso*propyl-(0,3,5)-bi*cyclo*-décane, nommé α-vétivane, obtenu par la méthode Wolff–Kishner[1] et par le procédé d'Adams.[2]

TABLEAU 1. COMPARISON DES CONSTANTES DU BI*cyclo*VÉTIVANE (X) ET DU 2,6-DIMETHYL-9-*iso*-PROPYL-(0,3,5)-BI*cyclo*DECANE

	Bi*cyclo*vétivane ce travail	α-vétivane[10]	
		1	2
Eb	79°5–80°	102°–103°	106°
sous (mm)	0,3	2,2	2,4
$d^{20}/_4$	0,8906	0,8919	0,8908
n_D^{20}	1,4810	1,4820	1,4812
$[\alpha]_D^{20}$	+3°12	−3°21	−3°12
RM_D obs.	66,52	66,54	66,54
calc.	67,17	67,17	67,17

* Echantillon préparé par M. A. Delsemme, Dissertation, Université Libre de Bruxelles.

[9] J. Pliva et F. Sorm, *Coll. Czech. Chem. Com.* **14**, 274 (1949).
F. Sorm, V. Herout et J. Pliva, *Usp. Khimii* **22**, 564 (1953).

[10] Y. R. Naves et E. Perrottet, *Helv. Chim. Acta* **24**, 1 (1941).

La concordance, au signe du pouvoir rotatoire près, des valeurs des constantes du bi*cyclo*vétivane et de l' "α-vétivane" est remarquable. De plus, pour l'un comme pour l'autre, on relève une même valeur, anormalement basse, de la réfraction moléculaire.

5. *Discussion. Structures du bi*cyclo*vétivénol* (I) *et du bi*cyclo*vétivène* (III)

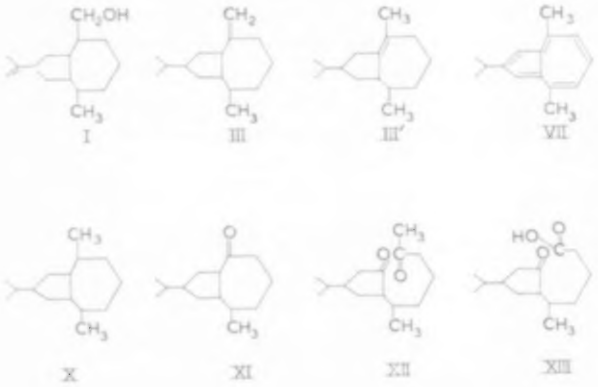
La nature des produits de déshydrogénation (VII) et de l'ozonolyse (XII et XIII) montre que le bi*cyclo*vétivène et, partant, le bi*cyclo*vétivénol (I) renferment un cycle pentanique et un cycle heptanique adjacents.[7]

L'examen des constantes physiques du bi*cyclo*vétivane (X) et l'application du procédé de Sorm à ce perhydrosesquiterpène confirment ce fait. L'emplacement des substituants est connu avec certitude: 2,6 (méthyles) et 9 (*iso*propyle).

Le chainon méthylène (III), où le groupe hydroxyméthyle (I) occupent la position 2 du cycle heptacarboné.

En fait, la pyrolyse de l'acétate de dihydrobi*cyclo*vétivénol livre un éthylénique partiellement transposé: III → III′. Par ozonolyse on obtient donc une *cyclo*heptanone (XI) (rupture de $\Delta^{2_0-2_1}$ de III) et une dicétone (XII) (rupture de Δ^{1-2} de III′), qu'une oxydation plus poussée, par BrO^-, transforme en dérivé XIII de la *cyclo*pentanone. La double liaison est très vraisemblablement localisée dans le groupe *iso*propényle. Il en résulte que le bi*cyclo*vétivénol possède la structure I, soit celle du 6-hydroxyméthyl-2-méthyl-9-*iso*propényl-(0,3,5)-bi*cyclo*décane.

Le bi*cyclo*vétivène, formé par la pyrolyse de l'acétate de dihydrobi*cyclo*vétivénol est donc le 2-méthylène-9-*iso*propyl-(0,3,5)-bi*cyclo*décane.



III. ÉTUDE STRUCTURALE DU TRI*CYCLO*VÉTIVÈNE. STRUCTURE DU TRI*CYCLO*VÉTIVÉNOL

1. *Tri*cyclo*vétivène*

Le tri*cyclo*vétivène obtenu par pyrolyse de l'acétate du dihydrotri*cyclo*vétivénol a été séparé sous forme de deux fractions (a) et (b) (voir §I.3).

Analyse: trouvé: Fr. (a): C = 88,44, H = 11,63; fr. (b): C = 88,37, H = 11,60. Calculé pour $C_{15}H_{24}$: C = 88,15, H = 11,15.

Ces fractions présentent les constantes indiquées ci-après. Leur spectre I.R. est reproduit dans la Fig. 4.

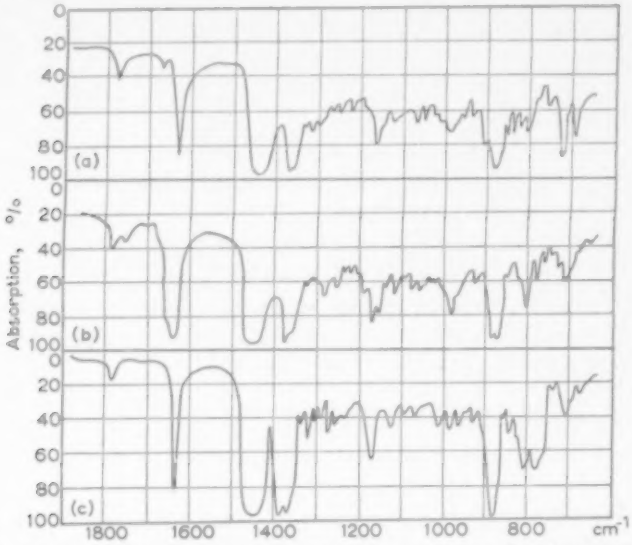


FIG. 4. Spectres I.R. des fractions (a) et (b) du tricyclovétivène (IV) (spectrographe double faisceau, cell. 0,080 mm) et du tricyclovétivène natif[4] [courbe (c); spectrographe simple faisceau cell. 0,025 mm.].

La comparaison des constantes physiques et des spectres I.R. des fractions (a) et (b) du tricyclovétivène (IV) avec les constantes et le spectre du tricyclovétivène natif, étudié récemment,[4] montre le lien de parenté existant entre les deux *cyclo*oléfines. Seules diffèrent les valeurs du pouvoir rotatoire.

Le spectre I.R. révèle, par ailleurs, que le tricyclovétivène (IV) obtenu par pyrolyse est un mélange d'isomères Δ^{20-21} et Δ^{1-2}, fait confirmé par l'étude de la dispersion du pouvoir rotatoire.

TABLEAU 2. CONSTANTES PHYSIQUES DU TRICYCLOVÉTIVÈNE

Constantes	Tricyclovétivène (IV)		Tricyclovétivène natif[4] de l'essence de vetiver
	fraction (a)	fraction (b)	
$Eb_{3,5}$	105° ± 1°	107° ± 1°	—
$d^{20/4}$	0,9318	0,9330	0,9340
n_D^{20}	1,5036	1,5052	1,5040
RM_D obs.	64,65	64,87	64,47
calc.	64,65	64,87	64,45
$[\alpha]_D^{20}$	+47°92	−3°52	+13°11

2. *Déshydrogénation du tricyclovétivène (IV)*

Le traitement du tricyclovétivène (IV) par du sélénium durant deux heures, a 280–300°, conduit à un déshydrogénat dont on isole une fraction azulénique (4%) et une fraction naphtalénique.

La première est du vétivazulène (VI): trinitrobenzénate $F = 147°5$, épreuve de mélange concluante avec un échantillon authentique de trinitrobenzénate de vétivazulène.

La fraction naphtalénique est de l'eudalène (VII): picrate $F = 90°5$, épreuve de mélange concluante.

3. *Ozonolyse du tricyclovétivène*

L'ozonolyse du tri*cyclo*vétivène (mélange d'isomères IV et IV' respectivement semicyclique et endocyclique) dans le tétrachlorure de carbone à $-5°$ fournit une fraction neutre.

Le spectre infra-rouge de celle-ci (0,006 M en solution dans le tétrachlorure) présente trois bandes fortes: 1748, 1718 et 1701 cm^{-1}. Un traitement à l'hypobromite à froid fait disparaître la dernière (méthyl*cyclo*alcoylcétone). On retrouve intactes les bandes en 1718 cm^{-1} (fraction neutre) et en 1745 cm^{-1} (fraction acide), caractéristiques des anneaux en C_6 et en C_5 respectivement.

4. *Hypothèses structurales*

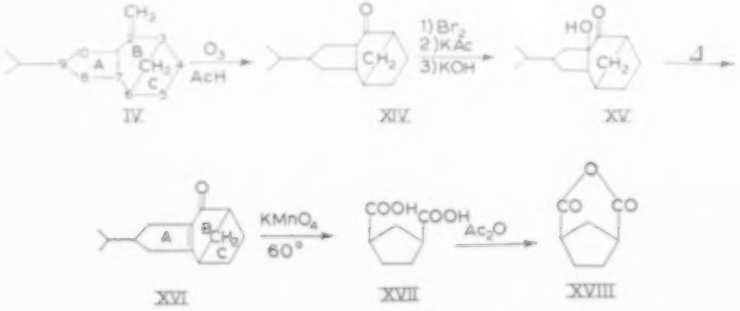
On possède, à présent, deux séries de renseignements concernant le tri*cyclo*vétivène (IV).

La déshydrogénation montre l'existence des anneaux pentacarboné et heptacarboné adjacents. Le premier (A) contient un groupe *iso*propyle en 9, le deuxième (B) comporte un groupe méthyle en 2 (il provient du chaînon méthylénique) et un autre en 6.

L'ozonolyse, elle, met en évidence les cycles pentanique et hexanique adjacents et, sur ce dernier, un groupe méthylène en 2. Il s'en suivrait que dans le tri*cyclo*vétivène (IV) le cycle en C_7 est non seulement fusionné au cycle en C_5 (A) mais est de plus compartimenté en deux anneaux: l'anneau hexacarboné (B) et l'anneau pentacarboné (C), par un pont endométhylénique partant du carbone n° 6 et aboutissant nécessairement* sur le carbone n° 3.

5. *Démonstration*

La dégradation du tri*cyclo*vétivène (IV) a été effectuée suivant le schéma ci-après:



La tri*cyclo*vétivène (IV) est ozonolysé en tri*cyclo*vétivanone (XIV)†. Celle-ci est transformée en cétone α,β-non saturée (XVII), par une suite d'opérations portant

* L'examen spectroscopique montre l'absence, dans le tri*cyclo*vétivène, d'anneau *cyclo*propanique.
† Comme précédemment[4] nous n'avons pu obtenir la semicarbazone de cette cétone.

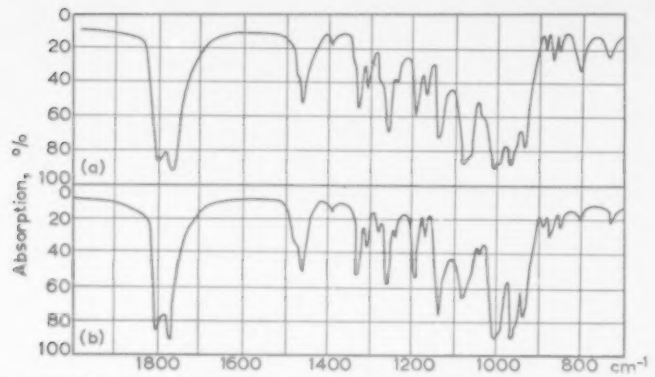


FIG. 5. Anhydride de l'acide *cis*-1,3-*cyclo*pentanedicarboxylique Spectre I.R. de l'échantillon de dégradation (a) et de référence (b) (spectrographe simple faisceau pastille KBr à 0,5%).

en α du C=O. L'on introduit successivement un brome, un groupe acétoxy, une fonction OH, pour déshydrater finalement l'hydroxycétone XV.

La cétone, α,β-non saturée est ensuite oxydée vigoureusement par le permamganate de potassium vers 60°. L'on sépare une fraction acide contenant XVII. Cette fraction est soumise à l'action de l'anhydride acétique.

Appliquant alors la chromatographie et la cristallisation fractionnée, nous avons isolé l'anhydride XVIII. Celui-ci fond a 159°5. Son spectre infra-rouge est identique au spectre de l'anhydride de l'acide *cis*-1,3-*cyclo*pentanedicarboxylique fondant à 159°5 (Fig. 5). L'épreuve de mélange entre l'anhydride formé par dégradation du tri*cyclo*vétivène et l'anhydride de l'acide *cis*-1,3-*cyclo*pentane dicarboxylique est concluante: fusion mixte à 159°5. Le cycle C est donc bien pentacarboné et il est lie au cycle B en méta.

6. *Tricyclovétivane. Test de Sorm*

L'hydrogénation du tri*cyclo*vétivène (fraction a) sur Ni–Ra à 100° et sous 50 atmosphères conduit au tri*cyclo*vétivane (XIX): $d^{20/4} = 0{,}9143$; $n_D^{20} = 1{,}4892$ $RM_D = 65{,}11$ (Calculé pour $C_{15}H_{26}$:64,97); $[\alpha]_D^{20} = +15°21$. Analyse: trouvé: C = 86,95; H = 12.65: calculé: C = 87,29; H = 12,71.

L'application du procédé de Sorm (Fig. 6) montre l'identité, à quelques bandes

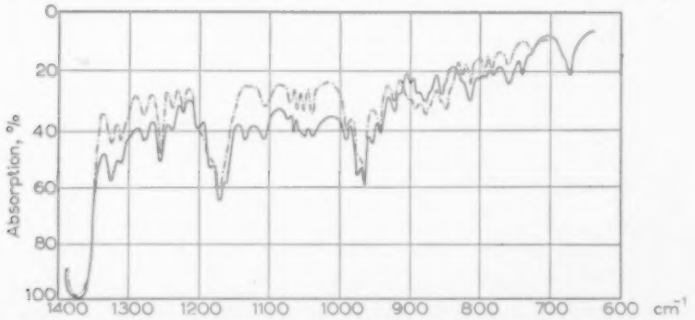
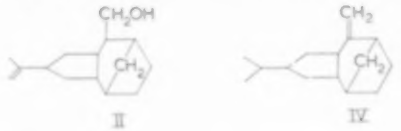


FIG. 6. Application du procédé de Sorm. Spectre I.R. du tri*cyclo*vétivane (XIX) obtenu dans ce travail (courbe en continu) (spectrographe double faisceau; cell. 0,10 mm) et du tri*cyclo*vétivane[4] (courbe en pointillé) (spectrographe simple faisceau; cell. 0,10 mm).

faibles près, des courbes d'absorption I.R. de notre échantillon de tricyclovétivane et de celui formé au départ du tricyclovétivène natif[4] et, partant, des deux cyclanes comparés.

7. *Conclusions*

Les expériences décrites plus haut permettent de conclure que la *cyclo*oléfine provenant de la pyrolyse de l'acétate de dihydrotricyclovétivénol est bien le 2-méthylene-9-*iso*propyl-3,6-endométhylène-(0,3,5)-bicyclodecane (IV), le tricyclovétivène. Le tricyclovétivénol primaire (II) de départ est, par conséquent, le 2-hydroxyméthyl-9-*iso*propényl-3-,6-endométhylène-(0,3,5)-bicyclodécane.



II IV

8. *Tricyclovétivénol primaire* (II)

Le traitement chromatographique de la fraction alcoolique primaire de l'essence de vetiver, étudiée plus haut, nous a permis d'isoler un échantillon de tricyclovétivénol primaire pur.

Analyse: trouvé: C = 81,86; H = 11,05; calculé: 81,75, H = 10,98.

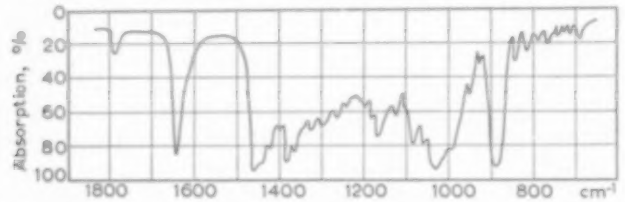


FIG. 7. Tricyclovétivénol primaire (II). Spectre I.R. (Spectrographe simple faisceau, cell. 0,050 mm).

Indice de non saturation (microhydrogénation): prise d'essai 177 mg, volume d'hydrogène absorbé (à 0° et 760 mm) 17,6 ml; calculé pour une double liaison: 18 ml.

L'examen du spectre I.R. de l'échantillon de tricyclovétivénol primaire séparé (Fig. 7) montre la présence d'une seule bande de double liaison. Elle est méthylénique: $\nu_{C=C}$: 1642 cm^{-1} et 890 cm^{-1}.

TABLEAU 3. CONSTANTES DU TRICYCLOVÉTIVÉNOL

	Ce travail	Semmler[5]	Ruzicka[6]
Eb_{13}		171°–174°	171°–172°
$d^{20/4}$	1,0105	1,0207	1,0212
n_D^{20}	1,5204	1,5252	1,5255
RM_D obs.	66,23		66,02
calc.	65,9		65,9
$[\alpha]_D$	+28°80	+34°30	+29°60

PARTIE EXPERIMENTALE

I. *Isolement d'un Échantillon de Tricyclovétivénol Primaire*

1. *Séparation*

L'huile brute de vetiver (100 g), après avoir été neutralisée, est chromatographiée sur gel de silice, préparé d'après Verzele.[11] Les rapports substance-adsorbant sont: 1/20, 1/40, 1/100. L'éluent est du benzène additionné de 0,25% de méthanol. On a isolé 4,4 g de tricyclovétivénol primaire. Les valeurs des constantes physiques de ce dernier sont indiquées dans le Tableau 3.

2. *Indice de non saturation du tricyclovétivénol*

La détermination de l'indice de non saturation a été faite par microhydrogénation d'après le procédé de Chiurdoglu.[8] Nous avons opéré en présence de Ni–Ra–W_7, en solution dans l'éthanol absolu. Prise: 0,177 g de tricyclovétivénol; volume d'hydrogène observé, à 0° et 760 mm de pression: 17,6 ml; volume calculé, dans les mêmes conditions, pour $C_{15}H_{24}O$: 18,0 ml.

II. *Séparation de la Fraction des Alcools Primaires de l'Essence de Vetiver*

1. *Séparation du mélange des acétates* (V/VI) *de bicyclovétivénol et de tricyclovétivénol*

Deux kg d'essence de vetiver débarrassées d'hydrocarbures et neutralisées sont traitées par deux litres d'anhydride acétique, à reflux, pendant trois heures. L'anhydride, en excès, est décomposé par l'eau et le produit réactionnel, repris dans l'éther, est neutralisé au bicarbonate de soude 10%. On sèche sur sulfate de magnésium. L'éther éliminé, on distille au moyen d'un coude et on obtient ainsi 1,3 kg de substance qui subit un tour de chromatographie sur 13 kg de gel de silice. L'élution se fait au moyen d'éther de pétrole. Les fractions de tête subissent ensuite un tour de distillation et fournissent 240 g de fraction hydrocarbonée $Eb_{0.5} = 75°–96°$. Deux tours de distillation complètent, d'autre part, la purification des acétates de bicyclovétivénol et de tricyclovétivénol primaires. ($Eb_{0.5} = 106°–115°$; $d^{20/4} = 1{,}0159$; $n_D^{20} = 1{,}5050$; poids = 975 g)

2. *Indice de non saturation du mélange des acétates* V/VI

On procède par microhydrogénation, comme plus haut. Prise d'essai: 0,289 g; volume d'hydrogène absorbé: 25,6 ml à 0° et 760 mm; calculé: 25,6 ml.

3. *Ozonolyse du mélange des acétates* V/VI

Dix grammes de ce mélange en solution dans 150 ml d'acide acétique glacial sont traités par un courant d'oxygène à 0,3% d'ozone. L'ozonide formé est détruit en refluant le produit réactionnel pendant 1 heure avec de l'eau (100 ml). Après neutralisation de l'acide acétique, on extrait la couche organique à l'éther et on sèche sur sulfate de magnésium. Apres évaporation de l'éther, le résidu visqueux (6,8 g) est soumis, à froid, à l'action de l'eau oxygénée à 5% (55 ml) en présence de carbonate de sodium à 10% (50 ml). Les aldéhydes susceptibles de se former sont ainsi éliminées. Apres 18 heures de traitement on sépare les fractions acide (2,0 g) et neutre (4,5 g). Dans la fraction neutre, on relève, en particulier, les bandes 1744 1737 et 1701 cm^{-1}.

[11] M. Verzele, *Bull. Soc. Chim. Belg.* **64**, 77 (1955).

La fraction neutre est ensuite pyrolysée à 450–500°, sous courant d'azote. Elle présente alors les bandes: 1744, 1722, 1715 et 1701 cm^{-1}. La fraction acide n'a pas été examinée.

4. cyclo*Vétivadiènes*

On pyrolyse 160 g du mélange des acétates V/VI à 500–550°, sous azote. Le diénique brut (72 g) subit un tour de chromatographie sur 750 g de gel de silice (éluant: éther de pétrole, fraction 60–80°). On obtient 58 g de mélange des *cyclo*vétivadiènes: $Eb_{0,2} = 66$–$69°$; $d^{20/4} = 0{,}9343$; $n_D^{20} = 1{,}5325$).

5. *Déshydrogénation des* cyclo*vétivadiènes*

On traite 18 g de dérivé diénique obtenu en §II.4 par du sélénium (10 g). On reprend par 50 ml d'éther de pétrole (40°–60°) et on extrait, à cinq reprises, par de l'acide phosphorique concentré (10 ml à chaque extraction). On sépare ainsi 0,4 g d'un dérivé azulénique. Celui-ci est du vétivazulène: son trinitrobenzénate fond à 147°5 sans accuser de dépression avec un échantillon authentique de trinitrobenzénate de vétivazulène*.

Le spectre U.V. de cet azulénique est le suivant: 350, 335, 293, 285, 245 mμ. Du déshydrogénat on isole, de plus, un naphtalénique dont le picrate fondant à 90°5 est identique au picrate de l'eudalène de référence. Le naphtalénique, libéré de son picrate, fournit un spectre I.R. identique à celui de l'eudalène.[12]

III. *Bi*cyclo*vétivène* (III) *et Tri*cyclo*vétivène* (IV)

1. *Mélange des acétates de dihydrobi*cyclo*vétivénol et de dihydrotri*cyclo*vétivénol*

L'hydrogénation sous 100 atmosphères de pression sur Ni–Ra à 100° d'un kg du mélange des acétates V/VI fournit environ 1 kg d'un mélange des acétates de dihydrobi*cyclo*vétivénol et de dihydrotri*cyclo*vétivénol.

2. *Pyrolyse du mélange des acétates des dihydroalcools*

Elle s'effectue, comme indiqué plus haut, vers 550° et sous azote. On chromatographie et on rectifie par distillation. On obtient 280 g d'un mélange de bi*cyclo*vétivène (III) et de tri*cyclo*vétivène (IV): $Eb_{0,1} = 53$–$59°$; $d^{20/4} = 0{,}9275$; $n_D^{20} = 1{,}580$.

3. *Ozonolyse du mélange de bi*cyclo*vétivène et de tri*cyclo*vétivène*

Dix grammes du mélange III/IV sont dissout dans 150 ml de tétrachlorure de carbone. On ozonolyse comme en II.3, à −5°. Le solvant est chassé par distillation et l'ozonide est décomposé par l'eau (2 heures) au bain-marie. Le résidu subit une oxydation par l'eau oxygénée à 5% (15 ml) en présence de carbonate de soude à 10% (48 ml) pendant 18 heures. On sépare 3,6 g de neutres se caractérisant dans l'I.R. par les nombres d'onde suivants: 1733, 1718 et 1701 cm^{-1}. On traite ensuite, durant deux heures, 2 g de neutres par une solution d'hypobromite formée comme suit: 20 ml d'eau, 3,6 ml de brome et 10 g de carbonate de soude. Après ce traitement, la fraction neutre fournit dans l'I.R. deux bandes de carbonyle: 1718 et 1701 cm^{-1}.

* Celui-ci nous a été obligeamment fourni par le Docteur I. R. Naves Directeur Scientifique de la firme Givaudan et Cie de Vernier—Genève (Suisse).

[12] J. Pliva, V. Herout, B. Schneider et F. Sorm, *Coll. Czech. Chem. Comm.* **18**, 500 (1953).

4. *Séparation du bicyclovétivène* (III) *et du tricyclovétivène* (IV)

Le mélange de *cyclo*oléfines III/IV formé en III.2 est soumis à une distillation fractionnée, afin d'en séparer les constituants. On opère à la colonne Todd au moyen d'un déphlegmateur de 20 plateaux théoriques, sous 3,5 mm de pression, stabilisée à 0,1 mm près. Au troisième tour de distillation, on obtient les fractions suivantes:

Le mélange contient environ un tiers de bi*cyclo*vétivène (III), $RM_D = 66,59$, le reste étant du tri*cyclo*vétivène.

Tableau 4. Fractionnement du melange III/IV, troisieme tour

Fraction n°	$Eb_{2,5}$	Poids (g)	Poids (%)	$d^{20/4}$	n_D^{20}	RM_D
1	80–103°	10,20	5,6	0,9337	1,5096	—
2	103–106°	40,50	22,3	0,9318	1,5036	64,65
3	106–108°	64,50	35,5	0,9330	1,5052	64,87
4	108–113°	62,40	34,3	0,9176	1,5041	66,50
Résidu		4,20	2,3			
Total		181,80	100,0			

* Comme précédemment[6] nous n'avons pu obtenir la semicarbazone de cette cétone.

IV. *Etude du Bicyclovétivène* (III)

1. *Bicyclovétivène* (III): $C_{15}H_{26}$ ($M = 206$)

Une rectification de la fraction 4 au moyen d'un déphlegmateur de 40 plateaux théoriques fournit le bi*cyclo*vétivène répondant aux constantes physiques légèrement modifiées: $d^{20/4} = 0,9170$; $n_D^{20} = 1,5046$; $RM_D = 66,59$. Le spectre I.R. est donné dans la Fig. 1.

2. *Indice de non saturation*

Le mode opératoire est défini en I.2. Prise d'essai: 100 mg volume d'hydrogène observé à 0° et 760 mm: 11,04 ml; calculé pour $C_{15}H_{26}$, 1/¯: 10,88 ml.

3. *Déshydrogénation*

Dix grammes d'hydrocarbures sont traités à 280–300° par 10 g de sélénium pendant 2 heures. Les procédés de séparation et de purification sont les mêmes que ceux utilisés plus haut (II.5).

(a) *Fraction azulénique*. Elle représente 14% de l'hydrocarbure de départ. Son trinitrobenzénate fond à 149°5 et ne donne pas de dépression avec un échantillon authentique de trinitrobenzénate de vétivazulène ($F = 150°$).

Spectre UV: 369, 350, 335, 325, 290, 284 et 246 mμ.

(b) *Fraction naphtalénique*. Elle représente 4% du produit mis en oeuvre. Le picrate correspondant fond, après six recristallisations dans l'éthanol, à 90–90°5. Ce picrate accuse un abaissement de 15° à l'épreuve de mélange avec le picrate de l'eudalène ($F = 90°5$). Le spectre I.R. du naphtalénique, libéré de son picrate, est reproduit

dans la Fig. 2. Son analyse indique qu'il s'agit d'eudalène accompagné de traces d'un deuxième naphtalénique.

4. *Ozonolyse quantitative du chaînon méthylénique*

On utilise le mode opératoire de Sorm.[13] 350 mg de bi*cyclo*vétivène fournissent ainsi 28,7% d'acide formique (11,4 ml de NaOH 0,00108 M) et 38,3% de formaldéhyde (48 mg de complexe avec la dimédone). Pas d'acétone. Au total: 67% de méthylène doublement lié.

5. *Examen I.R. du produit d'ozonolyse*

On traite 4 g de III comme en III.3 et on obtient 2,5 g de fraction neutre. Dans le spectre de ceux-ci, on relève dans la région de 1700 cm^{-1} les bandes fortes suivantes 1742, 1718 et 1706 cm^{-1}. Une partie de ces neutres (2 g) subit un traitement de 2 heures à l'hypobromite de soude (20 ml d'eau, 3,6 ml de brome, 10 g de carbonate de soude). Les fractions neutre et acide accusent, après ce traitement, les nombres d'onde $\nu_{C=O}$ que sont respectivement 1704 et 1745 cm^{-1}.

6. *Bi*cyclo*vétivane* (X)

L'hydrogénation sur Ni–Ra de 7 g de III, à 100° et sous 50 atmosphères, fournit après chromatographie et distillation fractionnée, 5 g de bi*cyclo*vétivane (X). Ses constantes physiques sont indiquées dans le Tableau 1 et son spectre I.R. est reproduit dans la Fig. 3.

V. *Etude du Tri*cyclo*vétivène* (IV)

1. *Tri*cyclo*vétivène*: $C_{15}H_{24}$ ($M = 204$)

Pour les constantes physiques, consulter le Tableau 2 et pour le spectre I.R., la Fig. 4.

2. *Déshydrogénation du tri*cyclo*vétivène*

Dix grammes de tri*cyclo*vétivène sont traités par 10 g de sélénium. Le mode opératoire et les procédés de séparation et de purification sont ceux décrits en §II.5.

Du déshydrogénat sont isolées deux substances. Ce sont:

(a) Le vétivazulène, identifié sous forme du trinitrobenzénate correspondant ($F = 149°5$) par épreuve de mélange avec un échantillon authentique de trinitrobenzénate de vétivazulène ($F = 150°$).

(b) L'eudalène, décelé par l'intermédiaire de son picrate ($F = 90$–$91°$) épreuve de mélange sans dépression avec un échantillon de référence (91°).

3. *Tri*cyclo*vétivane* (XI)

Dix grammes de tri*cyclo*vétivène (fraction a) sont hydrogénés en solution dans l'éthanol absolu, sur Ni–Ra à 100° et sous 5 atmosphères. Absorption: environ une molécule d'hydrogène. Le solvant est distillé et le résidu de distillation est rectifié ($Eb_{0,2} = 66$–$67°$) puis chromatographié sur gel de silice. On obtient 8,1 g de tri*cyclo*vétivane. Ses constantes physiques sont indiquées en § III. 6 et son spectre est reproduit dans la Fig. 6.

[13] F. Sorm, L. Dolejs, O. Knesse et J. Pliva, *Coll. Czech. Chem. Comm.* **14**, 699 (1949).

VOL. 4 1958

4. *Ozonolyse du tricyclovétivène* (IV)

L'ozonolyse a été pratiquée sur 10 g de tri*cyclo*vétivène en suivant le mode opératoire indiqué en §III.3. Dans les produits neutres (fraction a) résultant de l'ozonolyse on relève, dans la région de 1700 cm^{-1}, les bandes $\nu_{C=O}$ suivantes: 1748, 1718 et 1701 cm^{-1}. On traite la fraction (a) par une solution d'hypobromite et on obtient une nouvelle fraction neutre: $\nu_{C=O}$: 1718 cm^{-1} et une fraction acide $\nu_{C=O}$: 1748 cm^{-1}.

5. *Dégradation du tricyclovétivène* (IV)

(a) *α-bromotricyclovéntivanone*. On ozonolyse 75 g de tri*cyclo*vétivène et on obtient 30 g de tri*cyclo*vétivanone (XIV) ($Eb_{0.3}$ = 133–138°). La cétone est dissoute dans 300 ml d'éther anhydre et la solution, placée dans un ballon à trois cols, est traitée par 8 ml de brome, à −10°. L'addition se fait goutte à goutte, en attendant chaque fois la décoloration. L'addition terminée, on agite encore pendant 15 minutes puis on verse le mélange réactionnel dans l'eau glacée. La couche organique est séparée, neutralisée par une solution de bicarbonate de soude a 2% puis séchée sur sulfate de magnésium. L'éther est éliminé par distillation et on récupère le dérivé bromé (39 g) sous forme d'une huile brune.

(b) *α-hydroxytricyclovétivanone*. Le dérivé bromé est traité à reflux pendant 12 heures par une solution de 15 g d'acétate de potassium anhydre dans 90 ml d'acide acétique glacial. La réaction terminée, l'acide acétique est chassé sous vide. On ajoute de l'eau puis on extrait à l'éther. L'extrait éthéré est neutralisé au moyen d'une solution de carbonate de soude. Le solvant distillé, on obtient 28 g d'un produit huileux, l' α-acétoxytri*cyclo*vétivanone.

Celle-ci est chauffée à reflux pendant 7 heures avec une solution de 13 g de potasse dans 60 ml d'éthanol. L'extraction a l'éther permet finalement d'obtenir 12 g de l'α-hydroxytri*cyclo*vétivanone (XV).

(c) *Déshydratation de l'α-hydroxytricyclovétivanone*. L'hydroxycétone obtenue (12 g) est additionnée de 30 ml d'acide formique 98–100%. On laisse reposer 2 heures puis on chauffe au bain-marie durant 45 minutes. On dilue à l'eau, on neutralise au carbonate de sodium (solution 10%) et on extrait a l'éther de pétrole (60–80°). La majeure partie du solvant est chassée sous vide et le résidu est chromatographié sur 150 g de silicagel au moyen de benzène. On élue 4 g d'une huile brunâtre, caractérisée par son spectre I.R. comme une cétone α,β-non saturée.

(d) *Oxydation permanganique de la tricyclovétivénone* (XVI). L'oxydation de la tri*cyclo*vétivénone (XVI) se fait en milieu aqueux par 18 g de permanganate de potassium pulvérisé. La fraction acide huileuse qui en résulte représente environ 1 g.

(e) *Isolement et identification de l'anhydride de l'acide* cis-1,3-cyclo*pentanedicarboxylique* (XVIII). Cette fraction acide (1 g) est traitée pendant 1 heure par 10 ml d'anhydride acétique. Le produit de la réaction est chromatographié sur 50 g de silice, l'éluant étant du benzène. On sépare un solide jaunâtre. Celui ci, recristallisé jusqu'à point de fusion constant, se présente comme un solide blanc fondant à 159°5 + 0°5. Epreuve de mélange: un mélange de l'anhydride obtenu (159°5) avec un échantillon de l'anhydride de l'acide *cis*-1,3-*cyclo*pentanedicarboxylique (F = 159°5) fond à 159°5 + 0°5. Cette identité se vérifie encore au moyen de l'infrarouge. En effet, les spectres de l'anhydride de dégradation et de celui de référence sont superposables (voir Fig. 5).

6. *Préparation de l'anhydride de l'acide* cis-1,3-cyclo*pentanedicarboxylique*

Au départ de 5 g d'ester diéthylique de l'acide *cis*-1,3-*cyclo*pentanedicarboxylique* on forme 2,6 g d'acide *cis*-1,3-*cyclo*pentanedicarboxylique (XVII), $F = 120°$. Celui-est traité à reflux durant 1 heure avec 25 ml d'anhydride acétique. Il fournit après trois recristallisations dans l'anhydride acétique, 600 mg d'anhydride XVIII, $F = 159°5 + 0°5$, spectre I.R.: Fig. 5.

VI. *Spectres infra-rouges*

Les spectres I.R. ont été relevés à l'état liquide ou en solution, sur des spectrographes Perkin–Elmer 12 C (simple faisceau) et 21 C (double faisceau) munis d'un prisme en NaCl. Pour les cétones nous avons relevé les nombres d'onde en solution très diluée dans le tétrachlorure de carbone: 0,1 à 0,002 M/1.

VII. *Pouvoirs rotatoires*

Le pouvoir rotatoire du tri*cyclo*vétivénol a été mesuré à 20° en solution dans l'éthanol absolu: 26,425 g pour 100 g de solvant; $d^{20/4} = 0{,}8519$; tube: $l = 2{,}014$ dm, $\phi = 5$ mm.

Les autres pouvoirs rotatoires ont été pris à 20° dans un tube polarimétrique de 1,482 dm de longueur et 2,5 mm de diamètre. Les zéro de rotation ont été mesurés, dans chaque cas, à 20°, après avoir rempli les tubes polarimétriques d'eau distillée.

* Nous sommes reconnaissants envers le Docteur J. F. Birch, de la British Petroleum Co. qui a bien voulu nous procurer cet échantillon.

VOL. 4 195

Tetrahedron, 1958, Vol. 4, pp. 17–25. Pergamon Press Ltd., London

SOME RESULTS OBTAINED IN THE UTILISATION OF QUINONES AS PHILODIENE

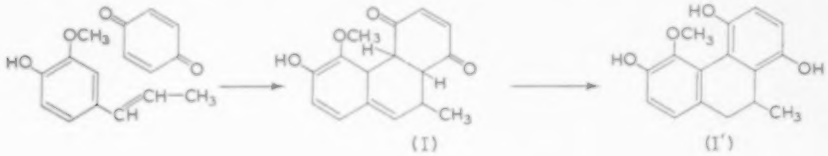
M. LORA-TAMAYO
Instituto de Quimica del C.S.I.C. y Universidad de Madrid Serrano 119, Madrid

(*Received* 9 *December* 1957)

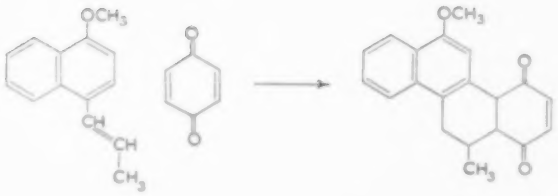
Abstract—In the course of a study of new applications of the Diels–Alder reaction, the addition of *p*-benzoquinone and substituted quinones to ethylene-aromatic dienes and heteroconjugations containing nitrogen, has been investigated.

Ethylene-aromatic conjugations

As the influence of the methoxyl group on the addition of maleic anhydride to ethylene-aromatic conjugations is already known,[1] a study of the behaviour of *p*-benzoquinone with eugenol[2] and 1:4-methoxypropenylnaphthalene[3] was undertaken; derivatives of phenanthrene (I) and chrysene(II) were obtained. In both cases diene and dienophile are added in a 1 : 1 proportion, and in the former the mobility of the hydrogen next to the =CO group is decisive in the isomerisation to the hydroquinone structure (I'). This is shown by the formation of an acetyl derivative.



(I) (I')

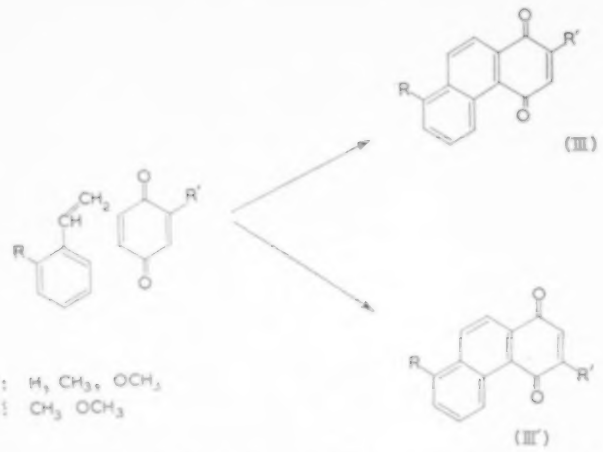


(II)

Results previously obtained in this laboratory with styrene and anethol[4] only led to copolymers when *p*-benzoquinone was employed, but substituted quinones (toluquinone and methoxyquinone), and styrene and its methoxy and methyl derivatives, gave 1 : 1-tetradehydrogenated adducts in which it has been shown that

[1] B. J. F. Hudson and R. Robinson, *J. Chem. Soc.* 715 (1941).
[2] M. Lora-Tamayo and D. G. Fernández Martin, *An. Fis. Quim.* **40**, 1178 (1944).
[3] M. Lora-Tamayo and D. G. Fernández Martin, *An. Fis. Quim.* **42**, 1083 (1946).
[4] M. Lora-Tamayo and J. M. Viguera, *An. Fis. Quim.* **38**, 192 (1942).

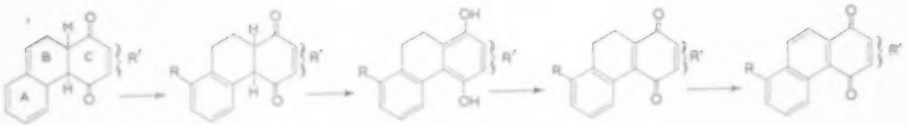
addition has taken place at the non-substituted dienophile double bond [(III) and (III')]:[5]



(III)

(III')

This tetradehydrogenation of the primary adduct is shown in the following scheme (IV) to (VIII):



(IV) (V) (VI) (VII) (VIII)

(V). Aromatisation of ring A, as shown in the adducts of maleic anhydride and with quinone.

(VI). Migration of the angular H atoms to the adjacent =CO groups, yielding a hydroquinone structure. This isomerisation is similar to that observed in the adducts of aliphatic dienes with quinones, and, even though it usually does not take place during addition, it can be achieved by using various reagents, such as acetic anhydride formation of the diacetate of the enolic form, traces of hydrobromic acid, traces of hydrochloric acid and stannous chloride, and by fusion.[6,7,8]

(VII). Oxidation to quinone, produced by toluquinone itself, which is to be found among the reaction products partially reduced to toluhydroquinone.

(VIII). Finally, aromatisation of the B ring by the toluquinone itself, leading to the tetradehydrogenated adduct, which can be isolated (cf. Johnson *et al.*,[9] Adams and Wicks[10] and Weizmann *et al.*[11]).

In support of this interpretation Johnson *et al.*[9] and Adams and Wicks[10] have studied the formation of tetradehydrogenated adducts 2:3-dimethoxybutadiene and from toluquinone or 2:3-dimethyl-*p*-benzoquinone. Similar observations have been made by Weizmann *et al.*[11] and Diels *et al.*[7] The loss of four atoms of hydrogen in the adduct excludes the existence of substituent R' in the angular position, which is inconsistent with the dehydrogenation mechanism, and suggests that the addition has taken place at the non-substituted double bond of the quinone. The quinonoid character of the adduct is indicated by oxime formation and also by reduction to the corresponding hydroquinone. Owing to the ease with which it oxidises, it was found preferable to reduce in presence of an acylating reagent (acetic anhydride,

[5] M. Lora-Tamayo, A. Alberola and C. Corral, *An. Fis. Quim.* B **53**, 63 (1957).
[6] K. Okahara and M. Suzuki, *J. Chem. Soc. Japan*, **63**, 1354 (1942). *Chem. Abstr*, **4**, 3088 (1947).
[7] O. Diels, K. Alder and G. Stein, *Ber. Dtsch. Chem. Ges.* **62**, 2337 (1929).
[8] L. F. Fieser and F. C. Chang, *J. Amer. Chem. Soc.* **64**, 2048 (1942).
[9] J. R. Johnson, W. H. Jobling and George W. Bodamer, *J. Amer. Chem. Soc.* **63**, 131 (1941).
[10] R. Adams and Z. W. Wicks, *J. Amer. Chem. Soc.* **66**, 1315 (1944).
[11] C. Weizmann, E. Bergmann and L. Haskelberg, *J. Chem. Soc.* 391 (1939).

acetic acid and zinc). The diacetates of the corresponding hydroquinones are obtained. The reaction with hydroxylamine hydrochloride agrees with Kehrmann's rule, according to which trisubstituted quinones only form mono-oximes.

Fieser[12] has synthesised 2-methoxy- and 3-methoxy-1:4-phenanthrene(III) and (III'), and the adduct from styrene and 2-methoxy-*p*-benzoquinone corresponds to (III) both in physical properties and in the products formed on alkaline hydrolysis.

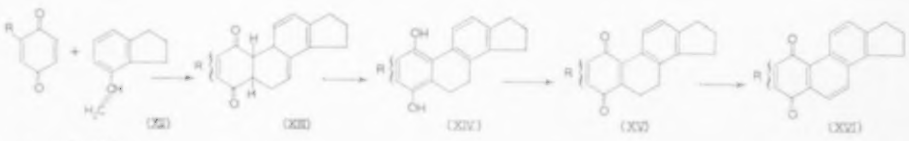
The reaction of styrene with *p*-benzoquinone did not yield a simple adduct. Kern and Feuerstein[13] obtained a compound the analysis of which indicated that it was formed from two molecules of styrene and one of *p*-benzoquinone, and assigned the structure (IX) to their product. The experimental facts adduced by Kern and

(IX)

Feuerstein can be readily explained if their compound is regarded as a styrene-*p*-benzoquinone (2:1) bis-adduct, which has lost eight hydrogen atoms. The compound would then be the result of a double dienic addition of the ethylene-aromatic conjugation of styrene to the two dienophilic unsaturations of *p*-benzoquinone. Of the two possible octadehydrogenated bis-adducts 1:2:5:6-dibenzoanthraquinone (X) and 1:2:7:8-dibenzoanthraquinone (XI), the former has been described[14] and appears to be identical with Kern and Feuerstein's compound.

(X) (XI)

In view of the biological interest of the *cyclo*pentenophenanthrene derivatives it was decided to study the reactions of quinones with 4-vinylindane (XII), and in every case a 1 : 1 adduct is obtained; the adduct from (XII) and *p*-benzoquinone corresponding to (XIII, R = H) decomposes at the m.p. 210°, losing 2H. It yields an acetyl derivative of (XIV),[15] but no oxime. The following scheme summarises the reactions:



(XII) (XIII) (XIV) (XV) (XVI)

R: H, CH_2OCH_3

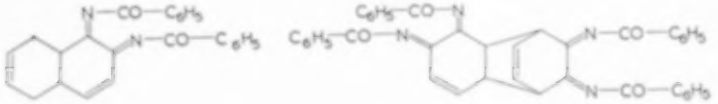
[12] L. F. Fieser, *J. Amer. Chem. Soc.* **51**, 1896 (1929).
[13] W. Kern and J. Feuerstein, *J. Prakt. Chem.* **158**, 186 (1941).
[14] R. Weitzenböck and A. Klinger, *Mh. Chem.* **39**, 315 (1918).
[15] M. Lora-Tamayo and J. Marín, *An. Fis. Quim.* B **48**, 693 (1952).

With the object of obtaining compounds with an angular methyl in (XIII), attempts were made to prepare the adduct from 4-vinylindane and 2-methyl-5-methoxy-*p*-benzoquinone (cf. refs. 16–21). After heating for 6–8 days only unchanged quinone could be isolated. This agrees with the interpretation put forward to explain the formation of tetradehydrogenated adducts.

Heteroconjugations containing nitrogen (cf. refs. 22–29)

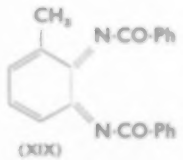
In view of Horner and Sturm's investigation[30] of *o*-quinones as "heterodienes" in the Diels–Alder reaction, it was decided to investigate the behaviour of *o*-quinone-di-imines, which may react with the ethylenic double bond in two ways, by addition to the heteroconjugation NH—C—C═NH (A) or the ethylenic conjugation (B):

Adams and co-workers[31,32] have shown that dienes such as butadiene form (1:1) adducts with *o*-quinonedibenzimide, e.g., (XVII), and also that *o*-quinonedi-imides are good dienophiles, e.g., (XVIII), which is regarded as an *o*-quinonedibenzimide dimer.



(XVII) (XVIII)

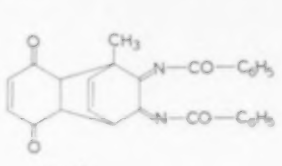
3-Methyl-*o*-quinonedibenzimide (XIX)[33] was prepared by the method of Adams and Way.[32]



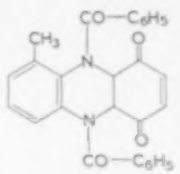
(XIX)

[16] M. Lora-Tamayo and C. Corral, *An. Fis. Quim.* B **53**, 45 (1957).
[17] L. F. Fieser and A. M. Seligmann, *Ber. Dtsch. Chem. Ges.* **68**, 1748 (1935).
[18] C.-K. Chuang and C.-T. Han, *Ber. Dtsch. Chem. Ges.* **68**, 876 (1935).
[19] A. Alder, *Ark. Kemi Min. Geol.* B **11**, 49 (1949).
[20] M. Orchin and L. W. Butz, *J. Org. Chem.* **8**, 509 (1943).
[21] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952).
[22] R. Pummerer and H. Fiesselmann, *Liebigs Ann.* **544**, 206 (1940).
[23] M. Lora-Tamayo and F. Fariña, *An. Fis. Quim.* B **48**, 91 (1952).
[24] M. Lora-Tamayo and J. Royo, *An. Fis. Quim.* B **48**, 81 (1952); M. Lora-Tamayo and F. Alvarez, *An. Fis. Quim.* B **48**, 75 (1952); M. Lora-Tamayo, R. Pérez Ossorio and M. Sanz Burata, *An. Fis. Quim.* B **50**, 865 (1954).
[25] F. Bergmann, *J. Amer. Chem. Soc.* **60**, 2811 (1938).
[26] G. La Paralo, *Gazz. Chim. Ital.* **64**, 919 (1934).
[27] G. Carrona, *Gazz. Chim. Ital.* **78**, 38 (1948).
[28] M. Lora-Tamayo and J. Fontán Yanes, *An. Fis. Quim.* **43**, 777 (1947).
[29] M. Lora-Tamayo and J. Fontán Yanes, *An. Fis. Quim.* B **44**, 583 (1948).
[30] L. Horner and K. Sturm, *Liebigs Ann.* **597**, 1 (1955).
[31] R. Adams and W. P. Samuels, Jr., *J. Amer. Chem. Soc.* **77**, 5357 (1955).
[32] R. Adams and J. W. Way, *J. Amer. Chem. Soc.* **76**, 2763 (1954).
[33] M. Lora-Tamayo and J. L. Soto Cámara, *An. Fis. Quim.* B **53**, 27 (1957).

(XIX) reacts with *p*-benzoquinone to form an adduct for which two structures are possible depending whether the addition takes place at the carbon conjugation (XX) or at the heteroconjugation —N=C—C=N— (XXI). Hydrolysis of the



(XX)



(XXI)

adduct yields benzoic acid, ammonia and a nitrogen-free now-crystalline product, for which the structure (XXII) is suggested, corresponding to (XX). Analysis and infra-red spectrum (see Fig. 1) are in agreement with the suggested structure. A

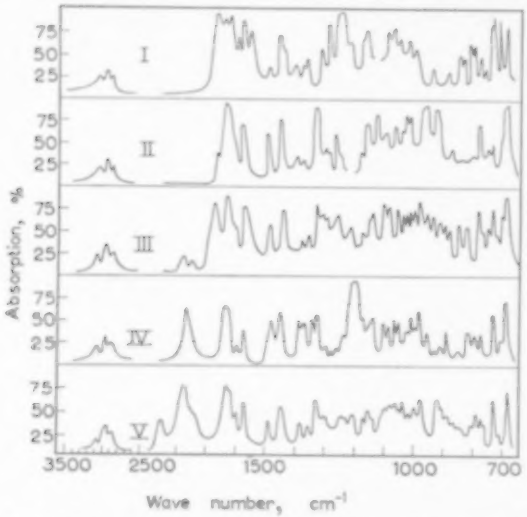
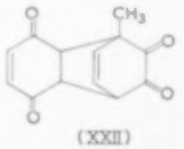


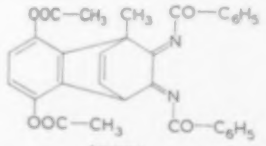
FIG. 1. Infra-red absorption spectra of: (I) 3-methyl-*o*-quinonedibenzimide dimer (red); (II) 3-methyl-*o*-quinonedibenzimide (white); (III) adduct of 3-methyl-*o*-quinonedibenzimide and and *p*-benzoquinone; (IV) acetylated derivative of the former; (V) adduct of 3-methyl-*o*-quinonedibenzimide and maleic anhydride. Determined with a Perkin–Elmer (model 112) spectrograph.

hydroquinone structure is inadmissible, since there are no bands in the spectrum of the adduct corresponding to —OH.

Acetylation of the adduct yields a diacetyl derivative (XXIII), which, as in the case of other quinone adducts, is probably formed after previous isomerisation of the adduct. Its infra-red spectrum also agrees with structure (XX).



(XXII)



(XXIII)

The most important feature of the spectra is the presence of the very intense 1635 cm^{-1} band in all of them, corresponding to an atomic group in every compound. The band is less intense in spectrum I of the dimer, which reveals another very intense band at 1666 cm^{-1}, which almost disappears in the monomer and is not found in the adducts. The 1635 cm^{-1} band is due to the C=O bond in the =C=N—CO—Ph group. The intensity of conjugation of C=O with the aromatic nucleus and the C=N bond explains the lowness of this band. Accordingly the C=O bond in =N—CO—Ph gives a band of a higher frequency, which would correspond to 1666 cm^{-1}. This explains why both bands appear in the red product (dimer), while the absence of the 1666 cm^{-1} band in the adduct spectra is determined by the addition of dienophiles to the carbon conjugation. The C=N groups are preserved and, consequently, the 1635 cm^{-1} band. The faint 1666 cm^{-1} band in the white product (monomer) must be due to traces of impurities in the dimer. A 1677 cm^{-1} band in spectrum III is due to the C=O of the quinone residue. In *p*-benzoquinone this band appears at 1665 cm^{-1} and, when one of the double bonds disappears, frequency increases slightly for conjugation decreases. The bands assigned to the C=O of the maleic anhydride adduct are in their normal position.

In no case do bands characteristic of the O–H and N–H bonds (3200–2500 cm^{-1}) appear, and therefore structures containing these groups can be discarded. The very intense deformation band (1515–1470 cm^{-1}) of the N–H group of the secondary amides does not appear. This supports the elimination of those structures containing the —NH—CO group.

EXPERIMENTAL

Adducts from styrene or 4-vinylindane and quinones. The mixture of diene and quinone in 1 : 2 molar proportions is heated at 100° (2 hr) in a closed tube or heated under reflux in toluene for 6–20 hr. A coloured solid is obtained, which is treated with ethanol to remove soluble impurities, and the residual adduct is purified by crystallisation from acetic acid or by sublimation. Table 1 summarises the adducts obtained.

Acetyl derivatives of the reduction products of adducts. The adduct (1 g), acetic anhydride (10 ml), glacial acetic acid (2·5 ml) and anhydrous sodium acetate (0·25 g) are heated under reflux, and zinc dust (1 g) is added in small portions during 1 hr. The colourless solution is poured into water, and the precipitated white solid and excess of zinc are filtered off, boiled with ethanol or acetic acid and again filtered, the acetyl derivative crystallising from the filtrate on cooling. In the case of the *iso*eugenol adduct, the triacetyl derivative was obtained by the usual method of acetylation without the addition of a reducing agent. Table 2 summarises the results obtained.

3-*Methyl*-o-*quinonedibenzimide* (XIX). This was prepared by oxidising 3-methyl-*o*-quinonedibenzamide with lead tetra-acetate, following the procedure of Adams and Way.[32] The product (7 g from 13·6 g of the dibenzamide) consists of red crystals mixed with a yellow powder, m.p. 126°, softening at 124–125, and is a mixture of monomeric and dimeric forms of the di-imide (Found: C, 76·55, 76·33; H, 4·82, 5·04; N, 8·67, 8·64. $C_{21}H_{16}O_2N_2$ requires C, 76·89; H, 4·88; N, 8·54 per cent. (*a*) M. wt. 345–346 (cryoscopic in benzene), corresponding to 6 per cent of the dimeric form; (*b*) 546 ± 30 (micro. Rast), corresponding to 60–75 per cent of the dimeric form). The determination was done on a red product, which on grinding

TABLE 1. ADDUCTS FORMED

Diene	Philodiene	Adduct			
		M.P. (°C)	Analysis		Formula
			Calculated (per cent)	Found (per cent)	
*iso*Eugenol[a]	*p*-Benzoquinone	215	C, 70·59; H, 5·88; OCH_3, 11·40	C, 70·4; H, 5·86; OCH_3, 11·4	$C_{16}H_{16}O_4$
1-Methoxy-4-propenylnaphthalene[b]	*p*-Benzoquinone	213	—OCH_3, 10·13	—OCH_3, 10·12	$C_{20}H_{16}O_3$
1-Methoxy-4-vinylnaphthalene	*p*-Benzoquinone	227–230	C, 78·2; H, 5·5; OCH_3, 10·6	C, 78·1; H, 5·3; OCH_3, 10·3	$C_{19}H_{16}O_2$
Styrene[c]	1:4-Toluquinone	141–142	C, 81·0; H, 4·54	C, 80·9; H, 4·61	$C_{15}H_{10}O_2$
Styrene[c]	2-Methoxy-*p*-benzoquinone	172	C, 75·6; H, 4·20	C, 57·7; H, 4·25	$C_{15}H_{10}O_3$
o-Methylstyrene[c]	2-Methoxy-*p*-benzoquinone	252 (dec.)	C, 76·1; H, 4·76	C, 76·1; H, 4·76	$C_{16}H_{12}O_3$
o-Methylstyrene[c]	1:4-Toluquinone	211·5	C, 81·3; H, 5·08	C, 81·2; H, 4·95	$C_{16}H_{12}O_2$
o-Methylstyrene	2-Methyl-5-methoxy-*p*-benzoquinone	—	—	—	—
o-Methoxystyrene[d]	1:4-Toluquinone	171–175	C, 76·2; H, 4·72	C, 76·3; H, 4·90	$C_{16}H_{12}O_3$
p-Methoxystyrene[d]	1:4-Toluquinone	218–219	C, 76·2; H, 4·72	C, 76·3; H, 4·96	$C_{16}H_{12}O_3$
m-Methoxystryrene[e]	1:4-Toluquinone	—	—	—	—
4-Vinylindane	*p*-Benzoquinone	210 (dec.)	C, 81·6; H, 5·60	C, 81·8; H, 5·64	$C_{17}H_{14}O_2$
4-Vinylindane[f]	1:4-Toluquinone	169·5–170	C, 82·4; H, 5·34	C, 82·4; H, 5·36	
4-Vinylindane[g]	2-Methoxy-*p*-benzoquinone	269	C, 77·6; H, 5·03	C, 77·5; H, 5·12	$C_{16}H_{14}O_3$
4-Vinylindane	2-Methyl-*p*-benzoquinone	—	—	—	—

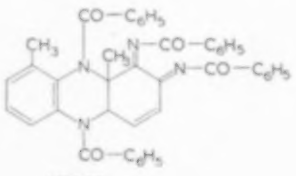
[a] Red coloured adduct from diene and deinophile (1 : 1).
[b] Crimson needles from diene and dienophile (1 : 1).
[c] Yellow tetradehydrogenated adduct.
[d] Red needles.
[e] Amorphous product, probably a polymer.
[f] Orange crystals from acetic acid. The adduct corresponds to 2- or 3-methyl-7:8-*cyclo*pentene-1:4-phenanthrenequinone. The adduct is a tetradehydrogenated addition product.
[g] Orange crystals from acetic acid, corresponding to 2-or 3-methoxy-7:8-*cyclo*pentene-1:4-phenanthrenequinone.[18]

TABLE 2. ACETYLATION OF THE REDUCTION PRODUCTS OF ADDUCTS TO GIVE DIACETYL DERIVATIVE

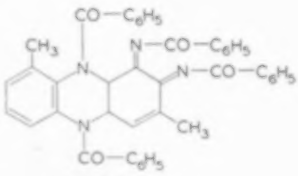
Adduct	Acetylated derivative		
	M.P. (°C)	Analysis	
		Calculated (per cent)	Found (per cent)
*iso*Eugenol-*p*-benzoquinone*	259	C, 66·3; H, 5·52	C, 66·9; H, 5·56
Styrene–1:4-toluquinone	139·5	C, 74·0; H, 5·19	C, 74·5; H, 5·45
Styrene–2-methoxy-*p*-benzoquinone	170	C, 70·3; H, 4·93	C, 70·4; H, 5·11
o-Methylstyrene–3:4-toluquinone	142	C, 74·5; H, 5·59	C, 74·5; H, 5·60
o-Methylstyrene–2-methoxy-*p*-benzoquinone	181	C, 71·0; H, 5·32	C, 70·9; H, 5·11
o-Methoxystyrene–1:4-toluquinone	175–178	C, 71·0; H, 5·32	C, 71·2; H, 5·51
p-Methoxystyrene–1:4-toluquinone	183	C, 71·0; H, 5·32	C, 71·2; H, 5·41
4-Vinylindane–1:4-toluquinone	177	C, 75·8; H, 5·74	C, 75·5; H, 5·81
4-Vinylindane–2-methoxy-*p*-benzoquinone	183	C, 72·5; H, 5·49	C, 72·4; H, 5·33

* Formed triacetyl derivative.

gave an intensely yellow powder. The red product on solution in a polar solvent (such as chloroform, methanol or ethanol) crystallised as a white solid, m.p. 126°, mixed m.p. with the red product 116–120° (Found: C, 76·27; H, 5·11; N, 8·54. $C_{21}H_{16}O_2N_2$ requires C, 76·89; H, 4·88, N, 8·54. M. wt. found 328; required 328). The red product (7 g) is converted to the white form by dissolving in hot ethanol (40 ml), from which it separates as a yellow crystalline mass, which after successive recrystallisations from ethyl acetate gave a white product, m.p. 126°. In solution it is unstable, gradually dimerising to the red form. Colourless solutions in benzene, chloroform or ethanol slowly turn yellow to orange, a change which is accelerated by heat. In the solid state the product is stable. The m.p. of 126° corresponds to the dimer, for it has been observed that 4–5° below this temperature the white product turns orange until 126°, when it begins to melt, the colour increasing in intensity. Evidence shows that (XIX) exists as a white monomer and a red dimer. The interpretation which Willstätter and Müller[34] advanced to explain the existence of white and red forms of the *o*-quinones as an example of structural isomerism between a peroxide (white) and ketonic (coloured) form cannot be applied to the present case. It is suggested that, if the dimer is formed by a Diels–Alder reaction in which one of the di-imide molecules behaves as a diene and another as a dienophile, the resulting adduct would be either (XXIV) or (XXV).



(XXIV)



(XXV)

[34] R. Willstätter and F. Muller, *Ber. Dtsch. Chem. Ges.* **41**, 2580 (1908).

Adduct (XX) *of 3-methyl-o-quinonedibenzimide and p-benzoquinone.* *p*-Benzoquinone (6 g) and (XIX) (9 g) in benzene (300 ml) are heated under reflux for 24 hr or left to stand for 30 days at room temperature. After removal of the benzene under reduced pressure, the residue is treated with ethanol to dissolve unreacted material and the adduct remaining (9·5 g, 79 per cent) is crystallised from ethyl acetate to give yellow needles, m.p. 237–238° (dec.). After repeated recrystallisations from ethyl acetate then was no gradual increase in m.p. (Found: C, 73·97; H, 4·36; N, 6·26. $C_{27}H_{20}O_4N_2$ requires C, 74·29; H, 4·61; N, 6·41 per cent). The adduct is soluble in benzene and dioxan, insoluble in ether and light petroleum and slightly soluble in warm ethanol. When the adduct (0·5 g) was heated under reflux with anhydrous sodium acetate (0·25 g) in acetic anhydride (10 ml) for 30 min, and the product was poured into cold water, the *diacetyl derivative* separated in crystalline form, which on repeated crystallisation from ethanol was obtained as colourless prisms, m.p. 196–198° (Found: C, 71·28; H, 5·23; N, 5·36. $C_{31}H_{24}O_6N_2$ (XXIII) requires C, 71·53; H, 4·61; N, 5·38 per cent). The adduct (1 g) was hydrolysed by being heated with concentrated hydrochloric acid (15 ml) and water (10 ml) under reflux for 30 min. The benzoic acid formed sublimed and a brownish red oil separated and solidified on cooling. The solid was washed with warm water to remove benzoic acid, and after drying the brownish red product weighed 0·5 g. After several crystallisations from ethanol the dark-coloured product melted at 145–147°, which is nitrogen-free, and does not react with 2:4-dinitrophenylhydrazine (Found: C, 68·32; H, 4·61. $C_{13}H_{10}O_4$ (XXII) requires C, 67·8; H, 4·16 per cent).

Tetrahedron, 1958, Vol. 4, pp. 26–35. Pergamon Press Ltd., London

SOME ASPECTS OF THE THERMOCHEMISTRY AND THERMODYNAMICS OF FLUOROCARBONS

C. R. PATRICK
Chemistry Department, The University, Birmingham 15

(*Received* 13 *December* 1957)

Abstract—The thermochemistry of some simple fluoro-compounds is discussed, and it is shown that the heats of formation of tetrafluoroethylene and of some 1:1-difluoroethylenes are anomalously low, suggesting a weakening of the double bond in these compounds as compared with that in more familiar ethylenes. This fact is shown to account for the high thermal stability of octafluoro*cyclo*-butane and of polytetrafluoroethylene.

VOL
4
195

THE considerable interest in fluorine-containing compounds, which is due in part to their high thermal stability, is backed by very little systematic thermodynamic data. It is the purpose of this paper to draw attention to some features of the information available.

The primary quantity to be determined is the bond-energy term for the C–F bond, and this can be derived from the heat of formation of carbon tetrafluoride. Several determinations have been made of the heat of formation of carbon tetrafluoride and the results are tabulated in Table 1. The more recent and more reliable

TABLE 1. HEAT OF FORMATION OF CARBON TETRAFLUORIDE

Value (kcal/mole)	Method of determination	Literature reference
−184	(Unspecified)	1
−162	Reaction of F_2 with charcoal (reaction did not proceed to completion)	2
−229 (corrected to graphite)	Fusion of K with CF_4	3, 4
−220·4	Reaction with F_2 with CH_4	5
−212·7	From heats of reactions: $C_2F_4 + 2O_2 \rightarrow CO_2 + CF_4$	6
−217·1	$C_2F_4 + 2H_2 \rightarrow 2C + 4HF$	7
−218·3	Combustion of Teflon–oil mixture	8
−218	Fusion of K with CF_4	9

[1] G. Glockler, *Fluorine Chemistry* (Edited by J. H. Simons). Academic Press, New York (1950).
[2] H. von Wartenburg and R. Schutte, *Z. Anorg. Chem.* **211**, 222 (1933).
[3] H. von Wartenburg, *Z. Anorg. Chem.* **258**, 356 (1949).
[4] H. von Wartenburg, *Nachr. Ges. Wiss. Göttingen* 57 (1946).
[5] R. S. Jessup, R. E. McCoskey and R. A. Nelson, *J. Amer. Chem. Soc.* **77**, 244 (1955).
[6] H. C. Duus, *Industr. Engng. Chem.* **47**, 1445 (1955).
[7] G. A. Neugebauer and J. L. Margrave, *J. Phys. Chem.* **60**, 1318 (1956).
[8] D. W. Scott, W. D. Good and G. Waddington, *J. Amer. Chem. Soc.* **77**, 245 (1955).
[9] F. W. Kirkbride and F. G. Davidson, *Nature, Lond.* **174**, 79 (1954).

values lie in the range $\Delta H_f(CF_4, g)$ −210 to −230 kcal/mole, and the value −218 kcal/mole seems to be a reasonable average for our purposes.

The controversy concerning the value of the heat of atomisation of carbon makes it impossible to calculate heats of atomisation and bond-energy terms that are universally acceptable. We have thought it advisable to duplicate many of our calculations by using the two more widely accepted values for the heat of atomisation of carbon, namely

$$L_c = 171{\cdot}7 \text{ kcal}^{10} \text{ (symbol } \alpha)$$
$$L_c = 138 \text{ kcal}^{11} \text{ (symbol } \beta)$$

Using these values, and the more recent value for heat of dissociation of fluorine, namely D(F–F) = 36·6 kcal/mole,[10] we obtain, respectively:

$$\alpha H_a(CF_4) = 463 \text{ kcal/mole}; \quad \bar{B}(C\text{–}F) = 116 \text{ kcal}$$
$$\beta H_a(CF_4) = 430 \text{ kcal/mole}; \quad \bar{B}(C\text{–}F) = 107{\cdot}5 \text{ kcal}$$

Owing to their acceptance of other values for $\Delta H_f(CF_4)$, previous authors have reported different values of $\bar{B}$(C–F). Thus Glockler[1] reports $\bar{B}(C\text{–}F) = 110$ kcal (α) and Cottrell[11] quotes $\bar{B}(C\text{–}F) = 94$ kcal (β), whereas Sidgwick[12] gives $\bar{B}(C\text{–}F) =$ 117·4 kcal (α). Long[13] uses the value $\Delta H_f(CF_4) = -229$ kcal,[3] but uses the old value $D(F\text{–}F) = 62$ kcal/mole.[14]

Sidgwick notes that his value of $\bar{B}$(C–F) from $\Delta H_f(CF_4)$ is much higher than that observed in compounds containing less fluorine, for which he gives the value $\bar{B}(C\text{–}F) = 103{\cdot}4$ kcal. That the increase of $\bar{B}$(C–F) with progressive fluorination is a real effect is suggested by the following considerations. The difference in the heats of formation (ΔH_f(RF) and ΔH_f(RH)) of two compounds differing only in substitution of a fluorine atom for a hydrogen atom is dependent chiefly on the difference in bond energy terms, namely:

$$\Delta = \Delta H_f(R\text{–}F) - \Delta H_f(RH)$$
$$= \bar{B}(C\text{–}F) - \bar{B}(C\text{–}H) - \tfrac{1}{2}[D(F\text{–}F) - D(H\text{–}H)]$$

Using data taken from a National Bureau of Standards circular,[10] we have calculated Δ for the cases tabulated in Table 2. The relationship for Δ applies strictly only when the heats of formation refer to the gas phase. We have not attempted to correct the available heats of formation to those for the gas phase, since insufficient information is available to enable this to be done easily or precisely. We consider that the errors that arise from ignoring this correction are very much smaller than the discrepancies in Δ. For these reasons we have not corrected data for both members of a pair of substances to the same state. An error of 2–3 kcal may arise in Δ from comparing solid and liquid substances.

Our results show that for the introduction of one fluorine atom into a hydrocarbon $\Delta \simeq -40$ kcal, whereas for the introduction of a second fluorine atom on to the same carbon atom $\Delta \simeq -50$ kcal. This indicates that the mean C–F bond energy in a difluoro compound is about 10 kcal greater than that in a monofluoro compound and that, whereas the former quantity is about 105 kcal, the latter must be about

[10] National Bureau of Standards, Circular 500 (1952).
[11] T. L. Cottrell, *Strengths of Chemical Bonds*. Butterworths, London (1954).
[12] N. V. Sidgwick, *Chemical Elements and their Compounds* Vol. II. Oxford University Press (1950).
[13] L. H. Long, *Quart. Rev. Chem. Soc.* 7, 134 (1953).
[14] H. von Wartenburg, G. Sprenger and J. Taylor, *Z. Phys. Chem., Bodenstein Festband* 61 (1935).

TABLE 2

Pair of substances	States (l = liquid, c = solid)	Heats of formation[10] (kcal/mole)	Δ (kcal)
(*a*) *Hydrocarbon and monofluoro compounds*—			
CH_3COOH	l	−116·4	−44·5*
CH_2FCOOH	c	−160·9	
CH_3CH_2OH	l	−66·4	−43·3
CH_2FCH_2OH	l	−109·7	
CH_3CONH_2	c	−76·6	−39·7
CH_2FCONH_2	c	−116·3	
(*b*) *Monofluoro and difluoro compounds*—			
CH_2FCOOH	c	−160·9	+26†
CHF_2COOH	l	−134·4	
CH_2FCONH_2	c	−116·3	−48·7
CF_2HCONH_2	c	−165·0	
CH_2FCH_2OH	l	−109·7	−51·7
CF_2HCH_2OH	l	−161·4	

* This value may be high by about 2 kcal, owing to our neglecting the differing states of the two substances.

† We consider that the value $\Delta H_f(CHF_2COOH)$ is incorrect, since the value of Δ that involves this quantity is so much out of keeping with the other estimates. This supposition is supported by the inconsistency of the following set of equations:

$$\Delta H_f(CH_3CONH_2) - \Delta H_f(CH_3COOH) = +40 \text{ kcal}$$
$$\Delta H_f(CH_2FCONH_2) - \Delta H_f(CH_2FCOOH) = +45 \text{ kcal}$$
$$\Delta H_f(CHF_2CONH_2) - \Delta H_f(CHF_2COOH) = -30 \text{ kcal}$$

115 kcal. Thus no appreciable difference in the bond energy appears to result from the introduction of the third and fourth fluorine atoms. These observations are in keeping with the shortening of the C–F bond in fluoromethanes noted by Pauling.[15]

In passing it is interesting to note that the results reported by Kirkbride and Davidson[9] for the heats of formation of chlorofluoromethanes, when plotted against flourine content, with the exception of the values for $\Delta H_f(CF_2Cl_2)$, lie close to a straight line, which also passes through the values for $\Delta H_f(CCl_4)$ and our selected value for $\Delta H_f(CF_4)$. This suggests that the C–F and C–Cl bond energy terms are nearly constant throughout the series, and that $\bar{B}(C\text{–}Cl) \simeq 77{\cdot}5$ kcal, as in simple chlorocompounds.

We can now consider the C–C bond-energy term in fluorocarbons. Kirkbride and Davidson[9] give for the heat of formation of hexafluoroethane $\Delta H_f = -303$ kcal/mole. Hence the heat of atomisation is:

$$\alpha H_a(C_2F_6) = 756 \text{ kcal/mole}$$
$$\beta H_a(C_2F_6) = 689 \text{ kcal/mole}$$

[15] L. Pauling, *Nature of the Chemical Bond*. Cornell University Press, New York (1945).

Using the values of $\bar{B}$ (C–F) obtained from H_a (CF_4), we have:

$$\alpha\bar{B}\,(\text{C–C}) = 61 \text{ kcal}; \quad \beta\bar{B}\,(\text{C–C}) = 44 \text{ kcal}$$

When compared with the values for hydrocarbons (α, $\bar{B}$ (C–C) = 83 kcal[16]; β, $\bar{B}$ (C–C) = 66 kcal[11]), these values appear very low. However the data for hydrocarbons[17] do not show a constant increment for each methylene group until hydrocarbons containing more than six carbon atoms are reached. The discrepancies in the C–H and C–C bond-energy terms involved are small, and, although a similar effect may occur in the fluorocarbon series, we do not consider that this will account for the present large disparity. We therefore suggest that the value for ΔH_f (C_2F_6) is low. Our suggestion has some support from the value for $\bar{B}$ (C–C) that we obtain as described below from the heat of formation of polytetrafluoroethylene.

The literature values for the heat of formation of polytetrafluoroethylene are −193·5[8] and ⇌199·9[6] kcal/mole C_2F_4. The latter value of the heat of formation of the polymer was determined on the basis of ΔH_f (CF_4) = −212·7 kcal/mole. We have recalculated this quantity directly from the results of the combustion given by Duus,[6] using ΔH_f (CF_4) = −218 kcal/mole, and we obtained ΔH_f (C_2F_4; polymer (*c*)) = −202·8 kcal/mole C_2F_4. This value is derived from data for a reaction at constant volume. The correction to constant pressure increases numerically the value by about 0·6 kcal/mole C_2F_4. Duus[6] found that the heat of formation of the heat-treated polymer had a (numerically) lower heat of formation as instanced by the value recalculated from his results on the basis outline above, namely ΔH_f (C_2F_4; polymer, (*c*) heat treated) = −200·9 kcal/ mole C_2F_4. This differs from that for the untreated polymer by about 2 kcal. The difference is the latent heat of fusion, since the fusion process is not reversed easily on cooling. We shall use a value:

$$\Delta H_f\,(C_2F_4;\ \text{polymer, } (c);\ \text{heat-treated}) = 196 \pm 5 \text{ kcal/mole } C_2F_4.$$

The published data for the heats of vaporisation of perfluoropentane[18] and perfluoroheptane[19] give for the increment (assumed constant) for the heat of vaporisation of linear perfluorocarbons at 25° the value 1·08 kcal/CF_2 group (which value is slightly smaller than that for hydrocarbons, 1·18 kcal/CH_2 group[20]). We may write therefore:

$$\Delta H_f\,(C_2F_4;\ \text{polymer, } g) = -194 \text{ kcal/mole}$$

whence:

$$\alpha H_a\,(C_2F_4;\ \text{polymer}) = 611 \pm 5 \text{ kcal/mole}$$

$$\beta H_a\,(C_2F_4;\ \text{polymer}) = 544 \pm 5 \text{ kcal/mole}$$

Since:

$$H_a\,(C_2F_4;\ \text{polymer}) = 2\bar{B}\,(\text{C–C}) + 4\bar{B}\,(\text{C–F})$$

we have, using our value of $\bar{B}$ (C–F) from H_a (CF_4):

$$\alpha\bar{B}\,(\text{C–C}) = 74 \text{ kcal}$$

$$\beta\bar{B}\,(\text{C–C}) = 57 \text{ kcal}$$

These values are about 10 kcal less than those that are found in hydrocarbons. In view of the small uncertainties in the heats of formation of the polymer, and of the

[16] G. E. Coates and L. E. Sutton, *J. Chem. Soc.* 1187 (1948).
[17] E. J. Prosen and F. D. Rossini, *J. Res. Nat. Bur. Stand.* **34**, 263 (1945).
[18] J. H. Simons and R. D. Dunlap, *J. Chem. Phys.* **18**, 335 (1950).
[19] G. D. Oliver and J. W. Grisard, *J. Amer. Chem. Soc.* **73**, 1688 (1951).
[20] F. S. Dainton, T. R. E. Devlin and P. A. Small, *Trans. Faraday Soc.* **51**, 1710 (1955).

uncertainty of equating $\bar{B}$(C–F) in the polymer to $\bar{B}$(C–F) in carbon tetrafluoride, we must conclude that $\bar{B}$(C–C) in fluorocarbons is close to, but probably smaller than, $\bar{B}$(C–C) in hydrocarbons. It is difficult to reconcile this observation with the mass-spectrometric estimates of 97 to 124 kcal/mole[21] for the dissociation energy, D(CF_3–CF_3), in hexafluoroethane, which are abnormally high when compared with D(C–C) values in hydrocarbons (about 80–87 kcal/mole[22]).

Three values are available for the heat of formation of tetrafluoroethylene, namely, −151·3,[6] −162,[9] and −151·7 kcal/mole.[7] The first value is associated with $\Delta H_f(CF_4) = -212{\cdot}7$ kcal/mole and comes from the heat of hydrogenation of tetrafluoroethylene. Using the data of Duus[6] for the combustion of tetrafluoroethylene, we find, assuming $\Delta H_f(CF_4) = -218$kc al/mole, that $\Delta H_f(C_2F_4) = -155$ kcal/mole.

We shall use the value $\Delta H_f(C_2F_4) = -152$ kcal/mole, which is close to the value (−151·7 kcal/mole) obtained in the most recent and most careful determination.[7] We have for the heat of atomisation:

$$\alpha H_a(C_2F_4) = 569 \text{ kcal/mole}$$

$$\beta H_a(C_2F_4) = 501 \text{ kcal/mole}$$

If we again use the value of $\bar{B}$(C–F) obtained from $H_a(CF_4)$ we can find $\bar{B}$(C=C). For comparison we tabulate (Table 3) also the values of $\bar{B}$(C=C) derived from $H_a(C_2H_4)$ and $H_a(CH_4)$, and $H_a(C_2Cl_4)$ and $H_a(CCl_4)$, using heats of formation given by the National Bureau of Standards.[10] Values are rounded to the nearest kcal.

TABLE 3. THERMOCHEMICAL DATA FOR LOW-SUBSTITUTED ETHYLENES

Compound	ΔH_f (kcal/mole)	$\bar{B}$(C–X)	$\bar{B}$(C=C)* (kcal) (α: $L_\alpha = 171{\cdot}7$ kcal)
C_2H_4	+12·5	98·8	142
C_2Cl_4	−3	78	149
C_2F_4	−152	116	105

* Similar differences arise when L_α is taken as 138 kcal.

These figures demonstrate an anomaly in the heat of formation of tetrafluoroethylene, which may conveniently be measured by the low value of $\bar{B}$(C=C) obtained for this compound when compared with other olefines. We shall show that this is of considerable importance in determining the properties of this compound, and that in particular it accounts for the high thermal stability of polytetrafluoroethylene and of perfluoro*cyclo*butane.

The weakness of the C=C bond in tetrafluoroethylene is also demonstrated by the ability of excited mercury atoms (Hg^3P_1) to dissociate the compound into two CF_2 radicals.[23] This requires that the dissociation energy of the double bond, D(CF_2=CF_2) is equal to, or less than, the energy associated with the energy of

[21] J. B. Farmer, I. H. S. Henderson, F. P. Lossing and D. G. H. Marsden, *J. Chem. Phys.* **24**, 348 (1955).
[22] M. Szwarc, *Chem. Rev.* **47**, 75 (1950).
[23] B. Atkinson, *J. Chem. Soc.* 2684 (1952).

excitation, that is 112 kcal/mole. This compares with the value of at least 130 kcal/mole required for the dissociation of the C=C bond in ethylene (see Cottrell[11]). Bond-dissociation energies are not simply related to average bond-energy terms. In any case the latter are dependent on the value used for the heat of atomisation of graphite. Clearly, however, changes in the one quantity must correspond to similar changes in the other. Bond-energy terms obtained by using $L_c = 171{\cdot}7$ kcal are closer to the observed bond-dissociation energies than are those obtained by using $L_c = 138$ kcal.

Weakening of olefinic double bonds seems to be associated with the presence of $=CF_2$ grouping. This is demonstrated by the values in Table 4, which are calculated from heats of formation of a number of compounds containing this grouping. The values of $\bar{B}$ (C=C) have been derived by using the bond-energy terms used previously.

TABLE 4. THERMOCHEMICAL DATA FOR FLUOROETHYLENES

Compound	ΔH_f (kcal/mole)	Literature reference	Heats of atomisation* (kcal/mole) (α: $L_c = 171{\cdot}7$)	$\bar{B}$ (C=C) (kcal/mole)
CF_2=$CFCl$	−126	9	553	127
CF_2=CH_2	−77·5	7	561	131
CF_3CF=CF_2	−259†	6	884	114‡

* Similar differences arise when L_c is taken as 138 kcal.

† Calculated from Duus's result:[6]

$$C_2F_4\,(g) \rightarrow \tfrac{2}{3}C_3F_6\,(g) + 20{\cdot}2 \text{ kcal},$$

using $\Delta H_f\,(C_2F_4) = -152$ kcal/mole.

‡ Calculated by using $\bar{B}$ (C–C) = 74 kcal, as estimated from polytetrafluoroethylene. This quantity may therefore be low by about 5 kcal.

The values of $\bar{B}$ (C=C) in these compounds lie about midway between that in tetrafluoroethylene and those found in other compounds.

In a series of papers by Lacher, Park and co-workers[24-27] the heats of bromination, chlorination and hydrobromination of a number of fluorinated olefines have been reported, and these differ markedly from those obtained with normal olefines. The authors observe that their results indicate anomalous bond-energy terms in the compounds concerned. This is demonstrated by the analysis of the results shown in Tables 5, 6, 7 and 8, in which the heats of saturation of the compounds are compared with the heats of saturation of ethylene. The heats of addition to tetrafluoroethylene are greater than those to ethylene and tetrachloroethylene by about 15–16 kcal/mole for all cases for which data are available. The heats of addition to chlorotrifluoroethylene are about 8 kcal/mole greater than those to ethylene. For other compounds containing the $=CF_2$ group the difference seems to be about 4–5 kcal/mole. These differences between the heats of addition parallel the differences between

[24] J. R. Lacher, J. J. McKinley, C. M. Snow, L. Michel, G. Nelson and J. D. Park, *J. Amer. Chem. Soc.* **71**, 1330 (1949); J. R. Lacher, J. J. McKinley, C. Walden, K. Lea and J. D. Park, *J. Amer. Chem. Soc.* **71**, 1334 (1949).

[25] J. R. Lacher, K. Lea, C. Walden, G. G. Olson and J. D. Park, *J. Amer. Chem. Soc.* **72**, 3231 (1950).

[26] J. R. Lacher, L. Casali and J. D. Park, *J. Phys. Chem.* **60**, 608 (1956).

[27] J. R. Lacher, A. Kianpour and J. D. Park, *J. Phys. Chem.* **61**, 584 (1957).

TABLE 5. HEATS OF ADDITION TO CF_2=CF_2 AND CH_2=CH_2 (kcal/mole)

Compound	Additive		
	HBr	Br_2	Cl_2
CF_2=CF_2	−32·99[25]	−38·48[26]	−57·32[24]
CH_2=CH_2	−16·8*	−23·8*	−41·5*†
Difference	16·2	14·6	15·8

* Here and elsewhere in these Tables heats of addition to ethylene are calculated from data given by the National Bureau of Standards[10] (T = 25°).

† It is interesting to note that the heat of chlorination of tetrachloroethylene is −41·1 kcal/mole.[10]

‡ These heats of addition were determined at about 90–130°. As elsewhere in this paper, no attempt has been made to correct the thermochemical data to a standard temperature. This is insufficient data to enable this to be done easily, but the correction involved is much smaller than the anomalies to be demonstrated.

TABLE 6. HEATS OF ADDITION TO CF_2=$CFCl$ AND CH_2=CH_2 (kcal/mole)

Compound	Additive		
	HBr	Br_2	Cl_2
CF_2=$CFCl$	−26·07[25]	−31·61[26]	−48·83[24]
CH_2=CH_2	−16·8	−23·8	−41·5
Difference	9·3	7·8	7·3

TABLE 7. HEATS OF ADDITION TO CF_2CCl_2 AND CH_2=CH_2 (kcal/mole)

Compound	Additive	
	HBr	Cl_2
CF_2=CCl_2	−22·05[25]	−41·08[24]
CH_2=CH_2	−16·8	−41·5
Difference	5·2	—

TABLE 8. HEATS OF CHLORINATION OF FLUORINATED OLEFINES

Compound	Heat of chlorination (kcal/mole)	Heat of chlorination of olefine − heat of chlorination of ethylene
CF_3CF=CF_2	−47·15[24]	−5·7
C_2F_5CF=CF_2	−44·97[27]	−3·5
C_3F_7CF=CF_2	−45·64[27]	−4·1
$(CF_3)_2C$=CF_2	−42·22[27]	+0·7

the bond-energy terms calculated above, but unfortunately there is no quantitative agreement. The smallness of these differences compared with the differences between the bond-energy terms may result in part from low values of $\bar{B}$(C–C) in highly fluorinated compounds, consistent with the trends shown by the single bond-energy terms we have calculated. Since heats of addition to olefines can be measured with greater accuracy than can heats of formation, the former provide a more reliable indication of bond-energy differences.

The C=C bond length in tetrafluoroethylene[28] is 1·31 Å, which is slightly shorter than that in ethylene[29] (1·33 Å). This shortening, which is significant, would normally be accompanied by an increase in binding energy. The C=C bond force constants in ethylene[30] and tetrafluoroethylene[31] are, respectively, 9·6 and $9{\cdot}2 \times 10^5$ dyn/cm. This suggests that the bond orders in the two compounds are about the same. The effects observed may be explained by supposing that the fluorine atoms withdraw electrons from the carbon atoms. One result of the reduction of electron density around the carbon atoms will be an increased repulsion between their nuclei, thus weakening the bond between them. Overlapping of the orbitals constituting the double bond may be made more difficult, and the slight shortening of the bond may be the means of correcting for this.

The C=C bond length in vinylidene fluoride[28] (1·31 Å) is about the same as that in tetrafluoroethylene. If the same effect persists in the $=CF_2$ structure, then a weakening of the C=C bond in this compound may arise in a manner similar to tetrafluoroethylene.

The partial transfer of electrons to the C–F bonds must also take place in saturated perfluoro structures, and may in a similar manner reduce the strengths of the C–C bonds.

We will now turn our attention to the stability of perfluoro*cyclo*butane and polytetrafluoromethylene. *cyclo*Butanes decompose primarily to ethylenes on heating, so that in discussing their stability we are concerned with equilibria of the type.

$$cyclo\text{-}C_4F_8 \rightleftharpoons 2C_2F_4$$

This equilibrium has been studied by Atkinson and Trenwith[32] in the temperature range 300-550°. The measured heat of reaction, −50·3 kcal/mole, compares well with that of −49·4 kcal/mole given by the results of Duus.[6] The experimental value of the entropy change (at 550°) is −49·2 e.u./mole, which compares with the value of −47·6 e.u./mole (at 298·2°K), calculated from the standard entropy of tetrafluoroethylene reported by Mann *et al.*[33] and that for perfluoro*cyclo*butane (the value of Furukawa *et al.*[34] for 261°K corrected to 298·2°K by using the specific heat data of Masi[35]). The corresponding quantities for the hydrocarbon series are −18·7 kcal/mole and −41·5 e.u./mole.[20] The heats of formation of partly fluorinated *cyclo*butanes from the corresponding ethylenes will have values intermediate between those quoted above, and this fact will be reflected in lower thermal stability of these

[28] I. L. Karle and J. Karle, *J. Chem. Phys.* **18**, 963 (1950).
[29] L. Pauling and L. O. Brockway, *J. Amer. Chem. Soc.* **59**, 1223 (1937).
[30] G. Herzberg, *Infra-red and the Raman Spectra*. Van Nostrand, New York (1945).
[31] Y. Morino, K. Kuchitsi and T. Shimanouchi, *J. Chem. Phys.* **20**, 726 (1952).
[32] B. Atkinson and A. B. Trenwith, *J. Chem. Soc.* 2082 (1953).
[33] D. E. Mann, N. Acquista and E. K. Plyler, *J. Res. Nat. Bur. Stand.* **52**, 67 (1954).
[34] G. T. Furukawa, R. E. McCoskey and M. L. Reilly, *J. Res. Nat. Bur. Stand.* **52**, 11 (1954).
[35] J. F. Masi, *J. Amer. Chem. Soc.* **75**, 5082 (1953).

butanes. We can predict that a compound of the form

$$\begin{array}{l} CF_2\text{—}CH_2 \\ | \qquad\; | \\ CF_2\text{—}CH_2 \end{array}$$

which may be prepared from ethylene and tetrafluoroethylene, will prefer to decompose into $CF_2{=}CH_2$.

Polytetrafluoroethylene decomposes almost exclusively to tetrafluoroethylene.[36] Other compounds detected in the decomposition products, particularly at higher pressures and temperatures, are products of subsequent reactions of the monomer. Results we have discussed give us for the heat of polymerisation of tetrafluoroethylene:

$$\begin{aligned} \Delta H_{gc} &= \Delta H_f \text{ (polymer, virgin)} - \Delta H_f \text{ (monomer)} \\ &= -198 - (-152) = -46 \text{ kcal}/C_2F_4 \text{ mole unit} \end{aligned}$$

The entropy of polytetrafluoroethylene cannot be specified at standard temperature (25°) on account of the second-order phase transition that takes place over the temperature range −20° to 40°. We shall, therefore, use the value at 340°K. The calorimetric entropy of the polymer at this temperature is[37] 28·95 e.u./C_2F_4 mole unit. We shall make no correction for the zero-point entropy, since this is likely to be small. Since the entropy of tetrafluoroethylene (1 atm) is 74·1 e.u./mole,[33] the entropy of polymerisation is:

$$\begin{aligned} \Delta S_{gc} &= 28{\cdot}95 - 74{\cdot}1 \\ &= -45{\cdot}1 \text{ e.u.}/C_2F_4 \text{ mole unit} \end{aligned}$$

Dainton and Ivin[38] have shown that the "crucial temperature," T_c, at which a polymer is in equilibrium with 1 atm pressure of its monomer, may with reasonable accuracy be predicted by using the expression:

$$T_c = \Delta H_{gc}/\Delta S_{gc}$$

in which the quantities are those at standard temperature. We may equally well use thermodynamic quantities at any other temperature. We have then:

$$T_c = 46{,}000/45{\cdot}1 \quad \text{or} \quad 1020°\text{K}$$

A more reasonable (but arbitrary) measure of polymer stability is the temperature at which a small pressure, say 10^{-2} atm (7·6 mm) of monomer will be supported over the polymer. Our entropy change would then be:

$$\begin{aligned} \Delta S_{gc}' &= \Delta S_{gc} + R \ln p \\ &= \Delta S_{gc} + R \ln 10^{-2} \\ &= -54{\cdot}3 \text{ e.u.}/C_2F_4 \text{ mole unit} \end{aligned}$$

Hence

$$T_c' = 850°\text{K} \quad \text{or} \quad \text{about } 580°\text{C}$$

In kinetic studies of the depolymerisation of polytetrafluoroethylene pressures of about 6 mm of monomer have been generated over the polymer[36] at 513°. Although this observation may have been made on a non-equilibrium system, we think it more likely that the discrepancy between this experimental observation and our calculated

[36] S. L. Madorsky, V. E. Hart, S. Straus and V. A. Sedlak, *J. Res. Nat. Bur. Stand.* **51**, 327 (1953).
[37] G. T. Furukawa, R. E. McCoskey and G. T. King, *J. Res. Nat. Bur. Stand.* **49**, 273 (1952).
[38] F. S. Dainton and K. J. Ivin, *Trans. Faraday Soc.* **46**, 331 (1950).

estimate is due to the incorrectness of our thermochemical data. There is some doubt about the correct value of ΔH_v. Indeed we have already observed that the heats of chlorination, bromination and hydrobromination of tetrafluoroethylene are about 16 kcal/mole greater than those for ethylene. A disparity of the same order is found when the heats of dimerisation of the two ethylenes are compared. Thus it would seem reasonable to suppose that the heat of polymerisation of tetrafluoroethylene would exceed that of ethylene by about the same amount. Using the value for ethylene of $\Delta H_{gc} = -24{\cdot}7$ kcal/mole,[20] we would estimate for tetrafluoroethylene $\Delta H_{gc} = -41$ kcal/mole, which is somewhat lower than the value used above. Nevertheless, we suggest that the polymer owes its high thermal stability to its unusually large heat of polymerisation. (Heats of polymerisation of most other olefines lie between -15 and -25 kcal/mole.) The polymeric radicals once formed by the moderately frequent rupture of bonds at about 400° and above, decompose in accord with their thermodynamic instability.

Acknowledgements—I thank Professor M. Stacey, F.R.S. and Dr. J. C. Tatlow for their kind encouragement during the preparation of this paper.

Tetrahedron, 1958, Vol. 4, pp. 36–42. Pergamon Press Ltd., London

STRUCTURE DE LA YANGONINE ÉTUDE SPECTROGRAPHIQUE DANS L'ULTRAVIOLET ET L'INFRAROUGE*

I. Chmielewska, J. Cieślak, K. Gorczyńska†, B. Kontnik† et K. Pitakowska†
Institut de Chimie Organique de l'Université de Varsovie, Pologne

(*Received* 8 *January* 1958)

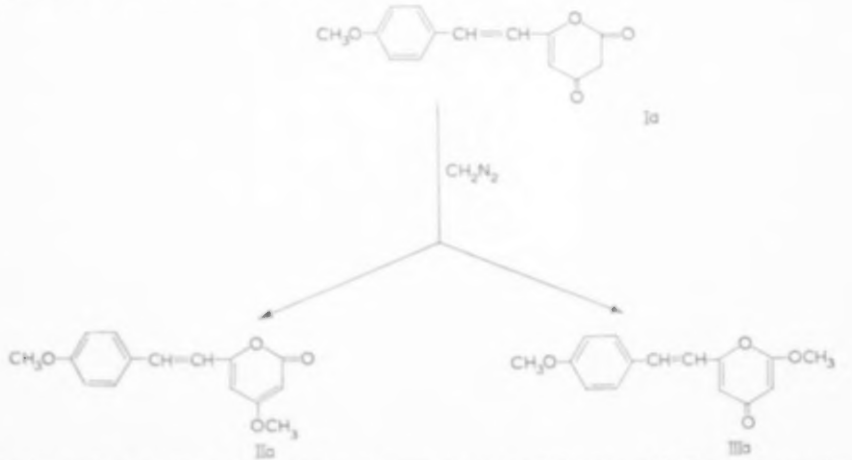
Résumé—On été exécutées les mesures d'absorption U.V. et I.R. de la yangonine (IIa), de la pseudoyangonine (IIIa) et des composés apparentés (IIb, c, d et IIIb, c, d). Les spectres d'absorption confirment la structure 4H-pyran-2-one de composés (IIa, b, c, d) et la structure 4H-pyran-4-one de composés (IIIa, b, c, d).

Abstract—The U.V. and I.R. absorption spectra of yangonine (IIa), pseudoyangonine (IIIa) and related compounds have been recorded. The absorption of the compounds of type II proves for their structure as 2H-pyran-2-one, and the absorption of the compounds of type III—their structure as 4H-pyran-4-one.

En 1914 Borsche et Gerhardt, se basant sur le comportement chimique et sur l'analyse des produits de sa dégradation, ont proposé pour la *yangonine*–colorant de la racine de *Macropiper methysticum* [Radix Kawa-Kawa] une structure de /*p*-méthoxystyryl/-6-méthoxy-2-pyrone-4 (IIIa).[1]

Cette formule a été généralement admise et jusqu'à présent ce colorant est cité dans la bibliographie comme le cas exceptionnel d'une méthoxy-2-pyrone-4 naturelle.

En 1929 Borsche et Bodenstein ont synthétisé la lactone yangonique (Ia) et, à partir de cette substance, un composé identique à la yangonine naturelle.[2] Leur formule, cependant, soulevant des objections, a été reéxaminée à l'Institut de Chimie Organique de l'Université de Varsovie.



* Une partie de ce travail a fait l'objet d'une communication préliminaire au 15e Congrès International de Chimie Pure et Appliquée, Paris, Juillet 1957.

† Laboratoire de Physique Technique de l'Institut de Chimie Générale, Varsovie, Pologne

[1] W. Borsche et M. Gerhardt, *Ber. Dtsch. Chem. Ges.* **47**, 2902 (1914).

[2] W. Borsche et H. Bodenstein, *Ber. Dtsch. Chem. Ges.* **62**, 2515 (1929).

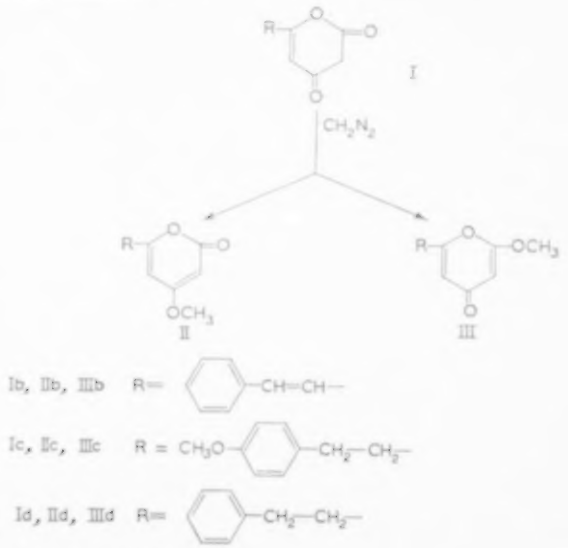
En 1939 Macierewicz a démontré que l'action du diazométhane sur un composé apparenté à la lactone yangonique, la styryl-6-dihydropyranedione-2,4, conduit à un éther identique à la méthoxy-4-pyrone-2 (IIb) obtenue par le procédé synthétique direct.[3]

En 1953 nous avons démontré que l'action du diazométhane sur la lactone yangonique donne un mélange des éthers isomères: *p*-méthoxystyryl-6-méthoxy-4-pyrone-2 (IIa) et *p*-méthoxystyryl-6-méthoxy-2-pyrone-4 (IIIa) qui diffèrent par leurs propriétés chimiques et physiques.[4]

La séparation a été effectuée par l'action de l'acide chlorhydrique gazeux qui précipite le composé ayant la structure méthoxy-2-pyrone-4 sous forme du sel insoluble dans l'éther tandis que la méthoxy-4-pyrone-2 libre reste en solution.

Les propriétés chimiques de ce dernier composé [$F = 153$–$154°$; chloroplatinate $F = 167$–$168°$] sont identiques à celles du composé synthétique de Borsche et Bodenstein ainsi qu'aux propriétés de la yangonine naturelle. L'autre éther, dont la structure IIIa a été admise par Borsche pour la yangonine, diffère au contraire du colorant naturel par ses propriétés physiques et chimiques [$F = 138$–$140°$; chloroplatinate $F = 151$–$153°$] Nous avons donné le nom de *pseudoyangonine* à ce composé.

Ces deux éthers isomères de la lactone yangonique appartiennent au groupe peu connu des dihydropyrane-diones-2,4. Jusqu'à présent, en dehors des composés cités ci-dessus, on ne connaissait que deux paires d'isomères de ce type: d'une part la méthoxy-4-coumarine et la méthoxy-2-chromone, obtenues par Arndt et Loëwe,[5] d'autre part la méthyl-6-méthoxy-4-pyrone-2 et la méthyl-6-méthoxy-2-pyrone-4, obtenues dans notre Institut.[6,7]



[3] Z. Macierewicz, *Roczniki Chem.* **24**, 144 (1950).

[4] I. Chmielewska et J. Cieślak, *Bull. Acad. Pol. Sci.* Cl. III Vol. I p. 257 (1953); *Roczniki Chem.* **28**, 38 (1954).

[5] F. Arndt et L. Loëwe, *Ber. Dtsch. Chem. Ges* **84**, 319 (1952).

[6] I. Chmielewska et J. Cieślak, *Przemysl Chem.* **8**, 196 (1952).

[7] I. Chmielewska, J. Cieślak et T. Kraczkiewicz, *Roczniki Chem.* **30**, 1009 (1956).

Nous avons ainsi été amenés à orienter la suite de nos recherches de façon à caractériser d'une manière plus précise la structure pyrone-2 de la yangonine. Pour réaliser ce but nous avons préparé trois lactones apparentées à la lactone yangonique: styryl-6-dihydropyrane-dione-2,4 [lactone desméthoxy-yangonique] Ib, $F = 245–246°$,[3] *p*-méthoxyphényl-2]-éthyl-6-dihydropyrane-dione-2,4 [lactone dihydroyangonique] Ic, $F = 181–182°$[8] et [phényl-2]-éthyl-6-dihydropyrane-dione-2,4 [lactone dihydrodesméthoxy-yangonique] Id, $F = 135–136°$.[8]

L'action du diazométhane sur la styryl-6-dihydropyrane-dione-2,4—la technique utilisée étant la même que dans le cas de la yangonine et de la pseudoyangonine—nous a conduits aux deux éthers isomères: styryl-6-méthoxy-4-pyrone-2 [desméthoxy-yangonine] IIb et styryl-6-méthoxy-2-pyrone-4 [desméthoxypseudoyangonine] IIIb. Le rendement a été, comme dans le cas précédent, 75% de pyrone-2 et 25% de pyrone-4. Le premier composé est identique au composé obtenu par Macierewicz.[3]

Les lactones dihydroyangonique et dihydrodesméthoxy-yangonique ont été soumises de même à l'action du diazométhane. Pour séparer les éthers isomères nous avons employé au début la méthode mise en oeuvre précédemment, mais elle s'est avérée insuffisante dans ce cas-là—nous n'avons pas obtenu de chlorhydrate solide de la pyrone-4 correspondante.

De bons résultats ont été obtenus au moyen d'acide perchlorique. La solution des éthers, triturée avec ce réactif, se trouble rapidement et après quelques minutes il se forme un précipité blanc, cristallin, du perchlorate de la pyrone-4 correspondante. L'éther isomère ayant la structure de la pyrone-2 reste en solution, d'où il peut être isolé après la séparation du perchlorate de la pyrone-4.

La pseudoyangonine et la desméthoxypseudoyangonine forment aussi des perchlorates stables, peu solubles dans l'éther. Les données caractéristiques des perchlorates obtenus sont reproduits dans le Tableau 1.

TABLEAU 1

Perchlorate de	Formule	Lactone utilisée (g/mole)	Perchlorate obtenu (g)	*F*
Pseudoyangonine	$C_{13}H_{14}O_4 \cdot HClO_4$	2,44/0,01	0,90	137° decomp.
Desméthoxypseudo-yangonine	$C_{14}H_{12}O_3 \cdot HClO_4$	2,14/0,01	1,04	135° decomp.
Dihydropseudo-yangonine	$C_{13}H_{16}O_4 \cdot HClO_4$	2,46/0,01	0,98	153–154°
Dihydrodesméthoxy-pseudoyangonine	$C_{14}H_{14}O_3 \cdot HClO_4$	2,16/0,01	0,94	142–143°

L'eau hydrolyse les perchlorates, libérant les pyrones-4, qui passent dans l'éther. Les détails expérimentaux sont décrits dans le travail précédent.[8]

Les rendement et points de fusion des éthers isomères obtenus sont rassemblés das le Tableau 2.

J. Cieślak, *Roczniki Chem.* **32**, à paraitre (1958).

TABLEAU 2

N	Substance	Formule	Lactone utilisée (g/mole)	Rendement (g)	Rendement (%)	F
IIa	Yangonine	$C_{15}H_{14}O_4$	2,44/0,01	1,92	75	153–154°
IIIa	Pseudoyangonine	$C_{15}H_{14}O_4$		0,64	25	138–140°
IIb	Desméthoxy-yangonine	$C_{14}H_{12}O_3$	2,14/0,01	1,56	71	139–140°
IIIb	Desméthoxypseudo-yangonine	$C_{14}H_{12}O_3$		0,70	29	123–125°
IIc	Dihydroyangonine	$C_{15}H_{16}O_4$	2,46/0,01	1,86	73	102–103°
IIIc	Dihydropseudo-yangonine	$C_{15}H_{16}O_4$		0,70	27	85–86°
IId	Dihydrodesméthoxy-yangonine	$C_{14}H_{14}O_3$	2,16/0,01	1,64	72	94–95°
IIId	Dihydrodesméthoxy-pseudoyangonine	$C_{14}H_{14}O_3$		0,64	28	46–47°

Le point de fusion de l'éther méthylique de la lactone dihydroyangonique qui ne forme pas de perchlorate, (IIc), est identique à celui de la dihydroyangonine, obtenue par Borsche par hydrogénation de la yangonine naturelle.[1]

Etude spectroscopique dans l'ultraviolet et l'infrarouge

Absorption ultraviolette. Les spectres U.V. des composée Ia, b, c, d, IIa, b, c, d et IIIa, b, c, d ont été mesurés avec un spectrophotomètre Beckmann DU. Les solutions dans l'éthanol à 95% à la concentration 10^{-5} étaient placées dans les cuves de quartz de 1 cm.

Les courbes d'absorption des lactones Ia, b, c, d sont presque identiques à ceux des composés IIa, b, c, d. Au contraire, l'examen des spectres permet de distinguer nettement les substances du groupe II des substances du groupe III.

Les spectres de la yangonine [λ_{max} 360 mμ, log ε 4,33; λ_{min} 280 mμ, log ε 3,75] de la desméthoxy-yangonine [λ_{max} 345 mμ, log ε 4,32; λ_{min} 275 mμ, log ε 3,82] diffèrent de ceux de la pseudoyangonine [λ_{max} 345 mμ, log ε 3,81; λ_{min} 290 mμ, log ε 3,63] et de la desméthoxypseudoyangonine [λ_{max} 330 mμ, log ε 3,80; λ_{min} 275 mμ, log ε 3,72] (Figs. 1 et 2). Les différences sont pourtant peu caracteristiques à cause du groupement styryle fixé en position 6 dans le noyau hétérocyclique.

Quant au spectre de la dihydroyangonine [λ_{max} 280 mμ, log ε 4,03; λ_{min} 245 mμ, log ε 3,37] et de la dihydrodesméthoxy-yangonine [λ_{max} 280 mμ, log ε 3,85; λ_{min} 250 mμ, log ε 3,14] ils diffèrent davantage de ceux de la dihydropseudoyangonine [λ_{max} 235 mμ, log ε 4,22] et de la dihydrodesméthoxypseudoyangonine [λ_{max} 240 mμ, log ε 4,25] (Figs. 3 et 4).

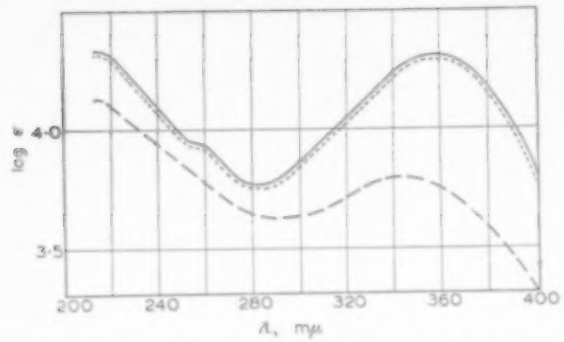


FIG. 1. Spectres d'absorption U.V. de la yangonine ——— , de la lactone yangonique . . . . . et de la pseudoyangonine – – – –.

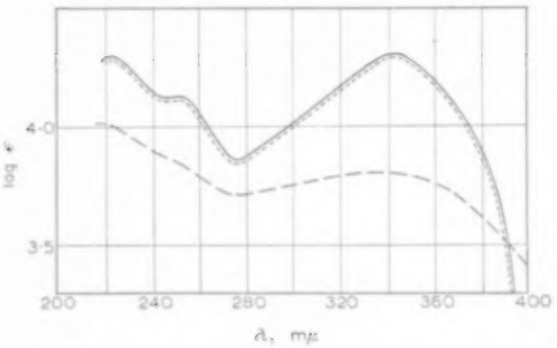


FIG. 2. Spectres d'absorption U.V. de la desméthoxy-yangonine ———, de la lactone desméthoxy-yangonique . . . . . et de la desméthoxy-pseudoyangonine– – –.

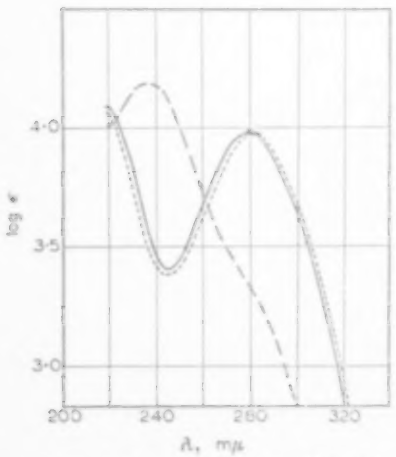


FIG. 3. Spectres d'absorption U.V. de la dihydroyangonine ——— de la lactone dihydroyangonique . . . . . et de la dihydropseudoyangonine – – – –.

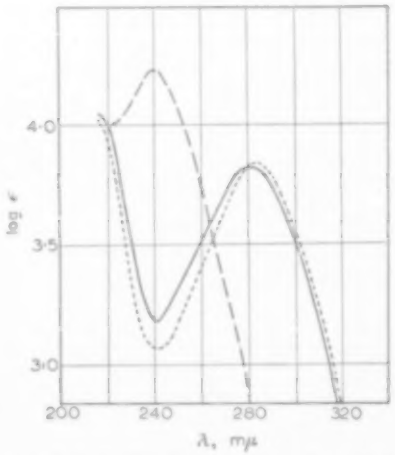


FIG. 4. Spectres d'absorption U.V. de la dihydrodesméthoxy-yangonine ———, de la lactone dihydrodesméthoxy-yangonique . . . . . et de la dihydrodesméthoxypseudoyangonine – – – –.

Les premières courbes d'absorption sont caractéristiques pour les pyrones-2, les secondes pour les pyrones-4. On observe les mêmes maxima dans le méthyl-6-méthoxy-4-pyrone-2 [λ_{max} 280 mμ, log ε 3,80; λ_{min} 240 mμ, log ε 2,94] et dans le méthyl-6-méthoxy-2-pyrone-4 [λ_{max} 240 mμ, log ε 4,12] obtenus par nous précédemment.[6] Il est intéressant de signaler l'analogie du spectre des méthoxy-4-pyrones-2 et des méthoxy-2-pyrones-4 étudiées et de ceux de la méthoxy-4-pyridone-2 et de la méthoxy-2-pyridone-4 qu'ont obtenus récemment par Den Hertog et Buurman.[9]

Absorption infrarouge. Les spectres ont été enregistrés de 2 à 12 μ sur un spectrophotomètre enregisteur Perkin–Elmer, modèle 21 muni d'un prisme de NaCl.

L'absence de la bande lactonique à 5,8 μ dans les spectres des lactones Ia, b, c, d (pastilles de KBr) s'explique sans doute par la chélation du carbonyle avec l'hydroxyle.

Les spectres de la yangonine, de la desméthoxy-yangonine, de la dihydroyangonine, et de la dihydrodesméthoxy-yangonine déterminés dans CCl_4 sont caractérisés principalement dans la région de 6 μ par la présence d'une forte bande à 5,8 μ [lactone éthylénique insaturée] et deux bandes à 6,05 μ et 6,45 μ.

La pseudoyangonine et la desméthoxypseudoyangonine en solution dans CCl_4 ont subis probablement une altération et leurs spectres ne sont pas caractéristiques. C'est pourquoi les mesures d'absorption de la pseudoyangonine ainsi que de la yangonine ont été exécutées dans le nujol. Ces spectres donnent des renseignements très précis sur la structure des composés III. L'absence de la bande à 5,8 μ et la présence de la bande à 6,0 μ [cétone ethylénique] indiquent une structure de pyrone-4. La bande dans la même position de 6,0 μ apparait aussi dans les spectres de la dihydropseudoyangonine et de la dihydrodesméthoxypseudoyangonine en solution dans CCl_4. La différence entre ces spectres et les spectres de la dihydroyangonine et de la dihydrodesméthoxy-yangonine est remarquable.

Absorption I.R.

Dans CCl_4. Yangonine 5,80; 6,06; 6,20; 6,45; 6,64; 6,90 7,15; 8,00; 8,53; 8,70; 9,63; 10,40; 10,45

Desméthoxy-yangonine 5,80; 6,06; 6,20; 6,45; 6,88; 7,12; 8,00; 8,70; 9,63; 10,00; 10,40

Dihydroyangonine 5,85; 6,07; 6,45; 6,60; 8,05; 8,48; 8,70; 9,70; 9,95; 10,53; 11,50; 12,10

Dihydrodesméthoxy-yangonine 5,85; 6,05; 6,40; 8,10; 8,80; 9,65; 10,60; 11,60; 11,95

Dihydropseudoyangonine 5,98; 6,10; 6,28; 6,60; 6,90; 7,18; 7,68; 8,03; 8,48; 8,68; 9,03; 9,25; 9,60; 10,85

Dihydrodesméthoxypseudoyangonine 6,00; 6,10; 6,28; 6,68; 6,90; 7,20; 8,00; 8,68; 9,33; 9,70; 10,88

Dans le nujol. Yangonine 5,80; 6,06; 6,25; 6,45; 6,60; 7,15; 7,95; 8,50; 8,70; 9,75; 10,45

Pseudoyangonine 6,00; 6,20; 6,40; 6,60; 7,10; 7,95; 8,48; 8,60; 9,75; 10,40; 10,85; 11,85

Conclusions

(1) Les propriétés physiques et chimiques de la yangonine naturelle sont identiques

[9] H. Den Hertog et D. Buurman, *Rec. Trav. Chim.* **75**, 257 (1956).

aux propriétés du composé IIa; celles de la dihydroyangonine sont identiques aux propriétés du composé IIc.

(2) Les propriétés physiques et chimiques de la yangonine naturelle diffèrent des propriétés du composé IIIa; celles de la dihydroyangonine diffèrent des propriétés du composé IIIc.

(3) Les spectres d'absorption en lumière U.V. et I.R. confirment la structure pyrone-4 de la pseudoyangonine et la structure pyrone-2 de la yangonine proposées par l'étude chimique.

Une partie de ce travail a été effectué par I. Chmielewska pendant un séjour à l'Institut de Chimie de l'Université de Zürich (juin-septembre 1957). Cet auteur exprime sa gratitude à Monsieur le Professeur P. Karrer pour son cordial accueil et le vif intérêt qu'il a montré pour le problème envisagé, ainsi qu'à Monsieur H. Frohofer qui a effectué les spectres I.R.

I. C. doit également des remerciements sincères au Ministère Polonais de Hautes Études qui a financé son séjour à Zurich.

Tetrahedron, 1958, Vol. 4, pp. 43–48. Pergamon Press Ltd., London

CHICORIC ACID (DICAFFEYLTARTIC ACID): ITS ISOLATION FROM CHICORY (*CHICORIUM INTYBUS*) AND SYNTHESIS

M. L. SCARPATI and G. ORIENTE
Institute of Organic Chemistry, Rome

(*Received* 17 *January* 1958)

Abstract—The isolation from the aqueous decoction of chicory leaves of a new optically active crystalline substance is described, for which the name chicoric acid is proposed. Experimental evidence indicates its structure as a caffeic diester of laevorotatory tartaric acid, which for the first time was found in nature in its (−)-form. Its synthesis, as well as that of laevorotatory and optically inactive isomers, was effected by the action of the chloride of carbonylcaffeic acid on D(−)-, L(+)- and *meso*-tartaric acids, respectively.

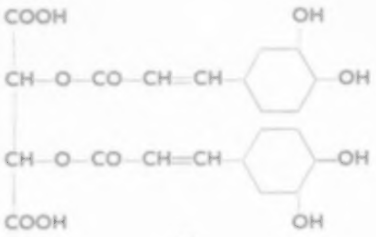
A CHROMATOGRAPHIC examination of the phenolic fractions of several plants[1] was carried out for the purpose of establishing the presence of cynarine and the chromatograms of chicory were found to be particularly interesting. In fact, when developed in 0·1 N hydrochloric acid, for example, they are characterised (as shown in Fig. 1)

FIG. 1. 1—Solution derived from the lead salts of chicory; 2—caffeic acid; 3—cynarine; 4—chlorogenic acid.

by the presence of two spots; the lower one, very intense, has an R_F inferior to those of caffeic acid, cynarine and chlorogenic acid. This spot should, therefore, correspond to a substance that is found in considerable quantities in chicory and is only slightly

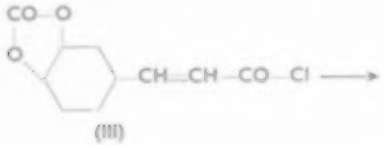
[1] M. L. Scarpati and G. Oriente, *Ann. Chim.* **47**, 155 (1957).

soluble in water, because of its low R_F value. Its isolation was easily accomplished by several extractions from the chromatographic solution with ether. From the ethereal extracts an amorphous substance is obtained, which crystallises from water in colourless needles, m.p. 206°. It is an acid of considerable strength for which the name chicoric acid is proposed. It is strongly dextrorotatory. Alkaline hydrolysis of chicoric acid in a hydrogen atmosphere gave caffeic acid (76 per cent) (I) and laevotartaric acid. This appears to be the first time that laevotartaric acid has been found in nature. The yield of caffeic acid indicates that chicoric acid is composed of two molecules of caffeic acid and one of laevotartaric acid, and this agrees with the analytical data corresponding with the molecular formula $C_{22}H_{18}O_{12}$, for which the structure (II) is proposed:

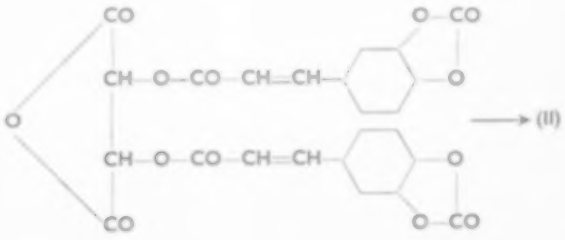


(II)

This structure is similar to those of other natural depsides such as chlorogenic acid (3-caffeylquinic acid) and cynarine (1:4-dicaffeylquinic acid),[2] in which the ester link occurs between the carboxyl of caffeic acid and the hydroxyls of hydroxy acid. Methylation of chicoric acid and subsequent hydrolysis gave two molecules of 3:4-dimethoxycinnamic acid, indicating that the four phenolic hydroxyls were free in chicoric acid. The synthesis of the latter was carried out by condensing two molecules of carbonylcaffeic acid chloride (III)[3] with laevotartaric acid.



(III)



A preliminary synthesis was carried out by condensing natural dextrorotatory tartaric acid with (III), which gave the antipode of chicoric acid. The ultra-violet and infra-red spectra of the natural product and of the two synthetic antipodes appeared to be identical (Figs. 2 and 3). Crystallisation of a mixture of equal

[2] L. Panizzi and M. L. Scarpati, *Gazz. Chim. Ital.* **84**, 792 (1954).
[3] L. Panizzi, M. L. Scarpati and R. Scarpati, *Gazz. Chim. Ital.* **84**, 812 (1954).

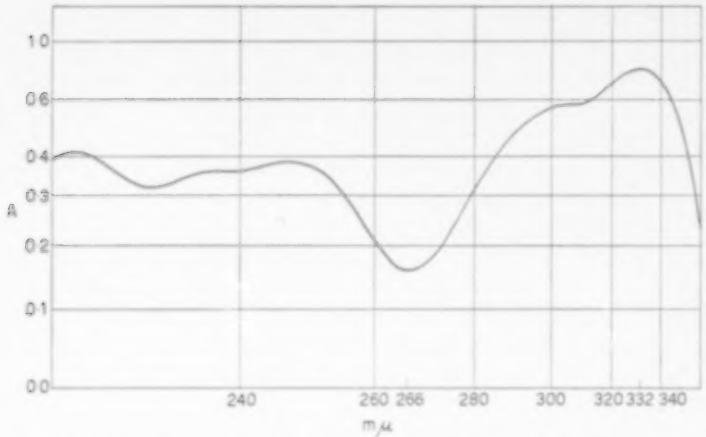


FIG. 2. Ultra-violet spectra: natural chicoric acid. The spectra of the dextro- and laevo-chicoric acids are practically identical.

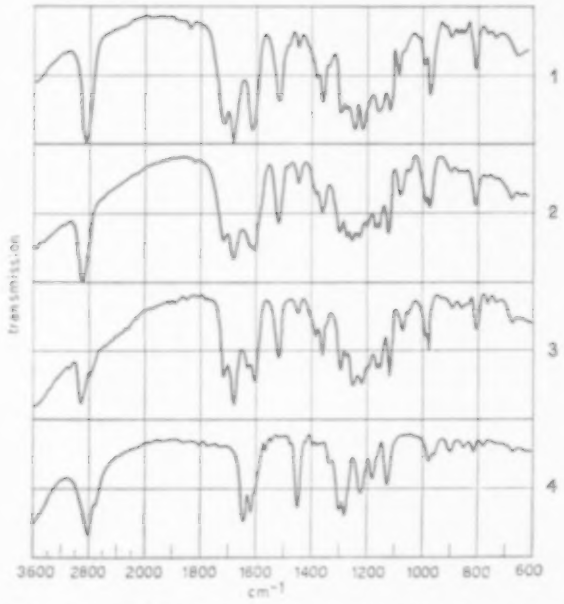


FIG. 3. Infra-red spectra (KBr): 1—dextrochicoric acid (natural); 2—laevochicoric acid (synthetic); 3—dextrochicoric acid (synthetic); 4—caffeic acid.

parts of natural dextrorotatory chicoric acid and synthetic laevorotatory chicoric acid gave *racemic* chicoric acid.

*meso*Chicoric acid was obtained by condensing (III) with *meso*tartaric acid. It differs in physical properties from the antipodes.

EXPERIMENTAL

Extraction of chicoric acid. 1000 g of chicory leaves, roughly chopped, are boiled for 1 to 2 hr in 5 l. of water, with occasional stirring. The decoction, decanted

and mixed with the liquid obtained by pressing the leaves, is filtered and precipitated with a 20% solution of neutral lead acetate. The gelatinous yellow lead salts are centrifuged, washed with water by centrifuging, suspended in 300 ml of water and decomposed with hydrogen sulphide. When the precipitation of the lead is completed, the liquid is heated on a steam-bath and filtered hot through a wide Buchner funnel, and the lead sulphide is washed with 50 ml of boiling water. The clear yellow filtrate is concentrated under reduced pressure on a steam-bath to 130 ml.

Two extractions, 80 ml of ether being used for each extraction, are sufficient to remove all of the chicoric acid, as shown by a chromatographic examination of the aqueous solution before and after the extractions.

After evaporation of the ether and drying under reduced pressure, an amorphous product is obtained which is very soluble in water. A 10% aqueous solution gently heated and decolorised with charcoal deposits almost pure chicoric acid as silky needles (0·4–1·1 g), m.p. 206°, $[\alpha]$ +383·5° (*c*, 1·555 in MeOH). (Found: C, 55·69; H, 4·02; equivalent, 231 (potentiometric) and 238 (titration with sodium hydroxide). $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent; equivalent, 237). The acid is soluble in ethanol, methanol, dioxan and acetone, slightly soluble in ethyl acetate and ether, and insoluble in ligroin, benzene and chloroform. It is very soluble in hot water but only 0·5 per cent soluble at 20°. It yields very soluble sodium salts, a slightly soluble barium salt and an insoluble yellow lead salt. With ferric chloride it gives an intense dark-green colour, and with alkalis a yellow colour, which changes in presence of air.

Alkaline hydrolysis of chicoric acid. Chicoric acid (2 g) is dissolved in 10 ml of boiling water in a flask provided with a reflux condenser. The air in the apparatus is displaced by a current of hydrogen and 30 ml of N sodium hydroxide is added and the mixture is heated for 1 hr. After cooling, 32 ml N hydrochloric acid is added and the acid solution is extracted with ether until the extract no longer gives a green coloration with ferric chloride. After removal of the ether the residue (1·52 g), which crystallises from water in iridescent tablets, m.p. 210°, was identified as caffeic acid (Found: C, 59·95; H, 4·64. Calc. for $C_9H_8O_4$, C, 60·0; H, 4·48 per cent). A mixed m.p. with an authentic specimen of caffeic acid showed no depression. The R_F in various solvents, solubility, crystalline form and ultra-violet and infra-red spectra corresponded to those of caffeic acid. From the acid solution after extraction of caffeic acid, tartaric acid (0·4 g) was obtained and analysed as the acid potassium salt (Found: C, 25·20; H, 3·07. Calc. for $C_4H_5O_6K$: C, 25·51; H, 2·78 per cent). 0·3 g of the acid was converted into pyruvic acid, which was identified as the 2:4-dinitrophenylhydrazone, m.p. 212° (dec.) (Found: N, 20·80. Calc. for $C_9H_8O_6N_4$: N, 20·89 per cent).

Methylation of chicoric acid. A mixture of chicoric acid (0·4 g), finely powdered potassium carbonate (3 g) and freshly distilled dimethyl sulphate (0·6 ml) in acetone (70 ml) was heated under reflux for 7 hr with exclusion of moisture, until the yellow colour of the mixture had faded. After filtration from the solid deposit of salts, and evaporation of the acetone filtrate under reduced pressure, the cold residue was mixed with benzene and shaken three times with 4 ml of 2 N sodium hydroxide to remove the products of incomplete methylation and excess of dimethyl sulphate. The benzene solution was washed with water, dried with anhydrous sodium sulphate and evaporated in a high vacuum until the residue had a constant

weight (0·4 g). Since the residue could not be crystallised, 0·368 g was hydrolysed by heating under reflux with ethanol (10 ml) and 30% sodium hydroxide (5 ml) for 4½ hr. After concentration to one-third of the initial volume and acidification with diluted hydrochloric acid (1:1), 0·271 g of 3:4-dimethoxycinnamic acid was obtained (theoretical for two molecules of the acid 0·275 g). Crystallisation from water yielded colourless needles, m.p. 178–179°, which showed no depression when mixed with an authentic specimen of 3:4-dimethoxycinnamic acid (Found: MeO, 29·5. Calc. for $C_{11}H_{12}O_4$: MeO, 29·8 per cent).

Laevorotatory chicoric acid. An intimate mixture of (III) (4·6 g) and (+)-tartaric acid (1·72 g) is heated under reduced pressure in a flask in a silicone bath. Reaction begins at 115° and the mixture fuses with evolution of hydrogen chloride. The temperature of the bath is raised to 135° for 10 min and then cooled. The white solid is heated with 80% acetic acid (90 ml) on a steam-bath until completely dissolved (40 min), and the solution is then evaporated under reduced pressure at 40°. The residue, consisting of chicoric acid and unchanged caffeic and tartaric acids, is heated with water (25 ml) at 50°. The mixture is filtered and the insoluble portion on chromatographic examination appears to be caffeic acid. The filtrate is twice extracted with ether (40 ml), which dissolves chicoric acid and any remaining caffeic acid, leaving tartaric acid in the aqueous layer. The ether layer is separated and evaporated, the residue is mixed with warm water (10 ml) and the pH is adjusted to 6 by addition of sodium hydrogen carbonate. Addition of saturated barium acetate solution precipitates the barium salt of chicoric acid, which is separated by centrifuging and washed with 3% barium acetate solution and then transferred to a separating funnel; 2 N hydrochloric acid (15 ml) and ether (40 ml) are added and the mixture is agitated until the solid has dissolved. The ether layer is removed and the aqueous layer is again extracted with ether (40 ml). The combined extracts are dried with anhydrous sodium sulphate and the ether is evaporated. The residue (2–2·5 g) is dissolved in warm water (20 ml), decolorised with charcoal and filtered. The acid crystallises in masses of tuft-like needles (1·5–1·9 g), m.p. 206°, and is identical with natural chicoric acid in every respect except the sign of the angle of rotation, [α] −384·2° (*c*, 1·075 in MeOH) (Found: C, 55·48; H, 3·99. $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent).

Racemic chicoric acid. This is obtained as pale-yellow needles by crystallising a mixture of natural dextrorotatory chicoric acid (0·2 g) and synthetic laevorotatory chicoric acid (0·2 g) three times from warm water. It has the same m.p. and R_F as the antipodes, [α] 0° (*c*, 1 in MeOH), but differs in solubility (0·1 per cent by weight in water at 20°).

Dextrorotatory chicoric acid. This is obtained by condensing (III) with (−)-tartaric acid, following the procedure for the laevorotatory acid. It was identical with the natural acid in every respect, [α] +384·6° (*c*, 0·988 in MeOH) (Found: C, 56·08; H, 4·03. $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent).

meso*Chicoric acid.* The product of condensation of (III) with *meso*tartaric acid, following the usual procedure, is finely powdered and heated on a steam-bath for ½ hr with 30 ml of 80% acetic acid, which dissolves the unreacted starting materials, the condensation product is filtered hot and dissolved in 80% acetic acid (90 ml). The same procedure is then followed as described previously. *meso*Chicoric acid crystallises from water as small lanceolate colourless crystals, m.p. 225°; the solubility in water is

0·11 per cent by weight at 20°; it is optically inactive and the sodium salt is sparingly soluble in water (Found: C, 55·18, 55·09; H, 4·08, 4·17. $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent).

Acknowledgement—We thank Dr. S. Califano of Naples University for kindly determining the infra-red spectra.

VOL.
4
1958

Tetrahedron, 1958, Vol. 4, pp. 49–67. Pergamon Press Ltd., London

ÜBER DIE EINWIRKUNG VON ALKALIHYDROXYDLÖSUNGEN AUF *o*-CHINOLACETATE

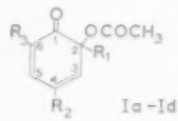
A. SIEGEL, F. WESSELY, P. STOCKHAMMER, F. ANTONY und P. KLEZL
Aus dem II. Chemischen Institut der Universität Wien

(*Received* 27 *January* 1958)

Zusammenfassung—Die Einwirkung von Alkalihydroxydlösungen auf *o*-Chinolacetate führt ausser zur Verseifung der Acetylgruppe in den meisten untersuchten Fällen auch noch zu weiteren Veränderungen des reaktionsfähigen Chinolsystems, wobei vor allem die beobachtete Aufspaltung des Chinolrings zu aliphatischen Verbindungen und die Bildung dimerer Verbindungen durch Additionsvorgänge bemerkenswert erscheinen. Der genetische Zusammenhang der verschiedenen Reaktionsprodukte konnte zum Teil hypothetisch angenommen, zum Teil experimentell gesichert werden.

Abstract—The interaction of alkali hydroxide solutions with acetates of *o*-quinols leads to further changes besides saponification of the acetyl group in most of the cases investigated. Especially noteworthy is the observed scission of the quinol ring to give aliphatic compounds and the formation of dimeric compounds by addition processes. The genetic connexion between the various products of reaction could be partly determined experimentally and partly assumed hypothetically.

DIE Versuche über die Einwirkung von wässrigen Alkalihydroxydlösungen auf *o*-Chinolacetate (I) wurden zunächst mit dem Ziel unternommen, aus diesen, durch Bleitetraacetat-Oxydation von geeigneten Phenolen gut zugänglichen Verbindungen[1] durch Verseifung die bisher nicht beschriebenen freien alkylsubstituierten *o*-Chinole zu erhalten. Unsere Untersuchungen, von denen wir Teilergebnisse bereits veröffentlichten,[2] zeigten aber, dass wohl eine derartige hydrolytische Abspaltung des Acetylrestes zu erreichen war, dass jedoch unter den Reaktionsbedingungen in den meisten Fällen nicht die erwarteten freien Chinole aufschienen, sondern vielmehr Substanzen, die ihr Entstehen weiteren Veränderungen des reaktionsfähigen Chinolsystems verdanken. Unter diesen Sekundärreaktionen ist besonders die hydrolytische Sprengung des Chinolringes unter Ausbildung aliphatischer Ketosäuren, bzw. entsprechender Laktone bemerkenswert, da sie eine unter abnorm milden Bedingungen vor sich gehende Spaltung eines carbocyclischen Ringsystems vorstellt.



Ia–Id

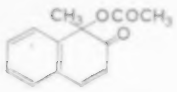
Ia: 2-Methyl-*o*-chinolacetat
$R_1 = CH_3$, $R_2 = R_3 = H$

Ib: 2-Phenyl-*o*-chinolacetat
$R_1 = C_6H_5$, $R_2 = R_3 = H$

Ic: 2,4,6-Trimethyl-*o*-chinolacetat
$R_1 = R_2 = R_3 = CH_3$

Id: 2,4-Dimethyl-*o*-chinolacetat
$R_1 = R_2 = CH_3$, $R_3 = H$

[1] F. Wessely und F. Sinwel, *Mh. Chem.* **81**, 1055 (1950) und weitere Arbeiten.
[2] F. Wessely, A. Siegel und P. Stockhammer, *Festschrift Arthur Stoll* 434 (1957); F. Antony, Dissertation, Universität Wien (1955); P. Stockhammer, Dissertation, Universität Wien (1957); P. Klezl, Dissertation, Universität Wien (1957).



Ie: 2-Methyl-3:4-benzo-*o*-chinolacetat

Ie

Im allgemeinen lassen sich bei den bisher von uns untersuchten *o*-Chinolacetaten (Ia–Ie) bei der Alkalieinwirkung drei Reaktionen unterscheiden: (*a*) die Verseifung der Acetylgruppe, (*b*) die hydrolytische Spaltung des Chinolrings und (*c*) weitere Umwandlungen der so gebildeten Produkte. Während die Reaktionen a und b bei allen untersuchten Ausgangsmaterialien, mit Ausnahme von (Ie), in gleicher Weise, wenn auch graduell verschieden abliefen, waren die mit c bezeichneten weiteren Reaktionsfolgen weitgehend von der Art und der Zahl der im ursprünglichen Chinolacetat anwesenden Substituenten, sowie von den bei der Alkalieinwirkung herrschenden Reaktionsbedingungen abhängig.

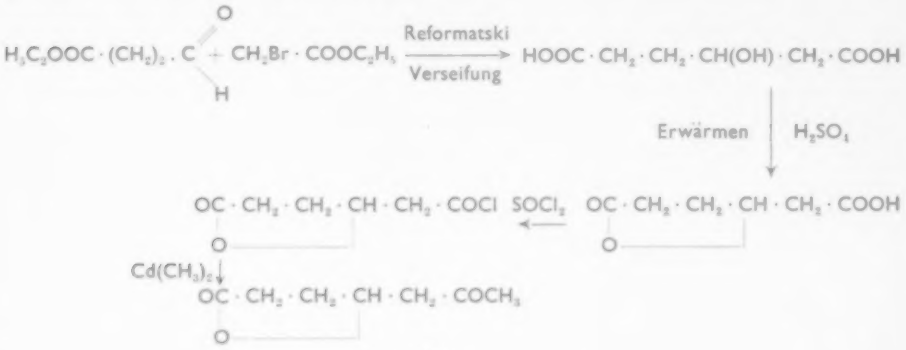
Die hydrolytische Abspaltung des Acetylrestes trat bei allen von uns untersuchten Fällen glatt und bereits bei sehr milden Bedingungen ein. Schon nach etwa 20 Minuten Stehen bei Zimmertemperatur mit der doppelten molaren Menge an 0,2 N Natronlauge waren in keinem Fall mehr wesentliche Mengen von unumgesetzten Chinolacetaten nachzuweisen, sofern bei den in Wasser schlecht löslichen Chinolacetaten durch Zusatz entsprechender Lösungsmittel (z.B. Äthanol) ein heterogenes System vermieden wurde. Quantitativ lässt sich hierbei das gebildete freie *o*-Chinol im Fall des 2-Methyl-3,4-benzo-*o*-chinolacetats (Ie) erhalten. Bei den nur mit Alkyl substituierten Chinolacetaten war jedoch eine präparative Isolierung des primär gebildeten freien *o*-Chinols mit Sicherheit nur beim 2,4,6-Trimethyl-*o*-chinolacetat (Ic) möglich, wo unter den im experimentellen Teil näher beschriebenen Bedingungen bei Zufügen einer alkoholischen Lösung des Chinolacetats zu wässriger Natronlauge nach entsprechender Aufarbeitung gelbe, bei 37–39° schmelzende Kristalle erhalten wurden, die auf Grund ihrer Analysenwerte, ihres UV- und ihres IR-Spektrums als 2,4,6-Trimethyl-*o*-chinol (IIc) anzusprechen waren.

Bei den drei anderen untersuchten Chinolacetaten konnte jedoch im Reaktionsgemisch das entsprechende freie Chinol nicht präparativ nachgewiesen werden. Die Hauptmenge der Reaktionsprodukte ist in diesen Fällen auf weitere Umwandlungen von primär gebildetem Chinol zurückzuführen.

Die oben erwähnte Spaltung des Chinolringes durch den Einfluss des Alkalihydroxyds wurde von uns zunächst beim 2-Methyl-*o*-chinolacetat (Ia) beobachtet. Schon die Tatsache, dass der durch Titration festgestellte Verbrauch an Hydroxylion in der Kälte bei 1,5 und in der Hitze bei etwa 1,9 Äquivalenten pro Mol. Chinolacetat lag, liess auf die Bildung von weiteren sauren Produkten neben Essigsäure schliessen.

Die präparative Aufarbeitung des, durch Einwirkung von wässrigem NaOH auf (Ia) bei 100° erhaltenen Reaktionsproduktes liefert neben einem weiter unten beschriebenen kristallisierten Stoff eine ölige Substanz der Molekularformel $C_7H_{10}O_3$. Aus dem Verlauf ihrer acidimetrischen Titration ergibt sich die Anwesenheit einer Laktongruppierung. Das dritte O-Atom liegt als Carbonylgruppe vor, wie durch Bildung eines Semicarbazons, sowie durch UV- und IR-Spektrum bewiesen werden konnte. Bei der Oxydation mit $KMnO_4$ werden Bernsteinsäure und Essigsäure gebildet. Die C-Methylbestimmung nach Kuhn–Roth liefert 1 Mol. Essigsäure.

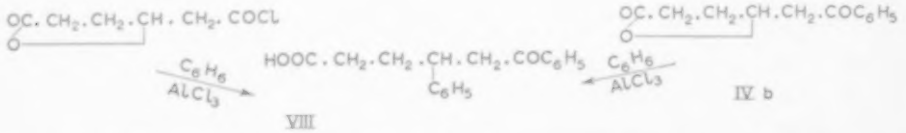
Bei der Behandlung dieses Ketolaktons mit Anisaldehyd in alkalischer Lösung erhielten wir unter Aufspaltung des Moleküls in guter Ausbeute Dianisalaceton. Diese Befunde ergeben für die ölige Substanz die Formel eines Laktons der 4-Hydroxy-heptanon-(6)-säure (IVa). Wir haben diese Verbindung daraufhin auf dem unten skizzierten Weg synthetisiert. Die Ausbeuten waren hierbei wohl, besonders bei der vorletzten Stufe sehr gering. Aber ein Vergleich der untersuchten chemischen und physikalischen Eigenschaften des synthetischen und des bei der Alkalieinwirkung auf (Ia) erhaltenen Laktons ergab deren Identität.



(IVa)

Auch aus dem 2-Phenyl-*o*-chinolacetat (Ib) kann ein der Substanz (IVa) analoges Lakton (IVb) erhalten werden, wenn man eine Dioxanlösung des Chinolacetats zu wässrig-methanolischer Natronlauge bei Zimmertemperatur langsam zutropfen lässt. Man erhält so nach entsprechender Aufarbeitung in einer Ausbeute von 30–40% eine weisse kristallisierte Substanz (IVb) vom Schmp. 124° und der Summenformel $C_{12}H_{12}O_3$. Die Konstitution dieser Substanz geht aus folgenden Reaktionen hervor:

(IVb) zeigt bei der Titration mit Lauge das Verhalten eines Laktons mit einem Äquivalentgewicht von 204. Weiters muss noch eine Ketogruppe im Molekül anwesend sein, da (IVb) eine positive Reaktion mit 2,4-Dinitrophenylhydrazin ergibt. Bei der Oxydation mit $KMnO_4$ konnten Bernsteinsäure und Benzoesäure festgestellt werden. Besonders charakteristisch für dieses Lakton ist aber—im Hinblick auf weiter unten folgende Überlegungen—die Tatsache, dass es mit 0,2 N NaOH zum Sieden erhitzt, eine Spaltung unter Bildung von Acetophenon erleidet. Aus diesen Befunden ergibt sich als Formel die eines Laktons der 4-Hydroxy-6-phenyl-hexanon-(6)-säure. Die angenommene Konstitution konnte noch durch die nachfolgenden Umsetzungen sichergestellt werden:



VIII IV b

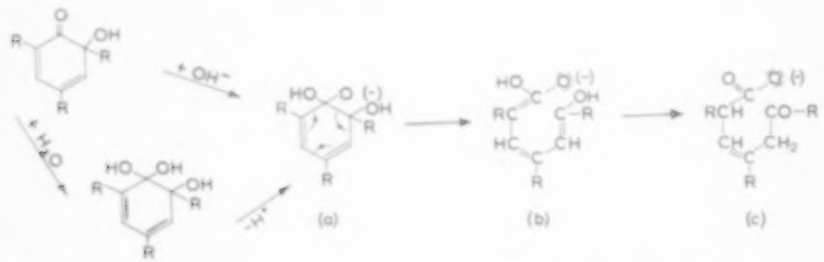
Kondensiert man das Chlorid des 3-Hydroxy-adipinsäure-laktons mit Benzol unter Einwirkung von $AlCl_3$, so treten sowohl die -COCl-Gruppe als auch die Laktongruppe in Reaktion und man erhält eine Substanz der Formel $C_{18}H_{18}O_3$, der die Struktur (VIII) zuzuordnen ist. Die gleiche Verbindung erhält man aber auch bei

der Kondensation von (IVb) mit Benzol und $AlCl_3$, wodurch dessen Struktur gesichert erscheint.

Im Fall des 2,4,6-Trimethyl-*o*-chinolacetats (Ic) erhält man bei der Laugeeinwirkung in der Kälte als Nebenprodukt, in der Hitze hingegen in praktisch quantitativer Ausbeute eine ölige Substanz (IIIc), der auf Grund ihrer Eigenschaften (Säurecharakter mit einem Äquivalentgew. 170, Bildung eines Semicarbazons, $C_{10}H_{17}O_3N_3$, Aufnahme von 1 Mol. Wasserstoff bei der katalytischen Hydrierung) die Struktur einer 2,4-Dimethyl-hepten-(3)-on-(6)-säure zukommt. Es bildet sich also hier nicht wie bei den vorhin erwähnten Chinolacetaten (Ia) und (Ib) das Lakton, sondern die entsprechende ungesättigte Säure. Das gleiche trifft auch für das 2,4-Dimethyl-*o*-chinolacetat (Id) zu, das bei der Alkalieinwirkung in der Hitze neben nicht aufgeklärten Produkten ein Öl bildet, dem wir die Konstitution einer 4-Methyl-hepten-(3)-on-(6)-säure zuschreiben. Allerdings ergibt hier die acidimetrische Titration Werte, die auf die Anwesenheit von etwa 20% des entsprechenden Laktons schliessen lassen. Auf die Trennung dieser beiden Substanzen sind wir nicht eingegangen.

Zusammenfassend lassen sich aus den bisher erläuterten Versuchsergebnissen über die ersten beiden Reaktionsschritte der Einwirkung von Alkalien auf die untersuchten Chinolacetate folgende Schlüsse ziehen:

Das bei der Einwirkung von Alkalihydroxyd in wässriger Lösung auf *o*-Chinolacetate als primäres Reaktionsprodukt anzunehmende freie *o*-Chinol erleidet im allgemeinen eine sofortige weitere Umwandlung, wobei es zu einer Aufspaltung des Chinolrings kommt. Über den Mechanismus dieser Aufspaltung lassen sich natürlich nur Hypothesen aufstellen, doch scheint uns der folgende Reaktionsweg am ehesten den experimentellen Befunden zu entsprechen:



Die Bildung des angenommenen ersten Zwischenproduktes, des Ions a, lässt sich entweder durch eine Anlagerung eines OH-Ions an die CO-Doppelbindung des Chinols deuten, oder aber durch eine Protonenabgabe der Hydratform des Chinols. Die letztere Möglichkeit ist deswegen mit in Betracht zu ziehen, da einerseits die Existenz solcher Hydratformen in wässriger Lösung durch UV-Spektroskopie von Derkosch und Kaltenegger[3] nachgewiesen werden konnte, anderseits aber, wie weiter unten näher ausgeführt, in überwiegend alkoholischen Lösungen—wo also mit der Anwesenheit von Keto-Halbacetal zu rechnen ist—an Stelle der Säuren bzw. Laktone die entsprechenden Ester erhalten werden können.

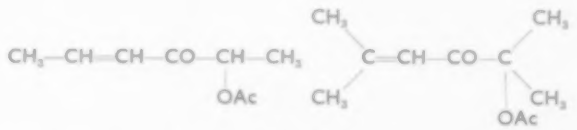
Der nächste Schritt unseres angenommenen Reaktionsschemas besteht in einer Verlagerung des π-Elektronensystems in der angedeuteten Richtung, wodurch es zur Ausbildung des Ions b kommt, das Dienolcharakter besitzt und dessen tautomere

[3] J. Derkosch und W. Kaltenegger, *Mh. Chem.* **88**, 778 (1957).

Diketo-Form die Konstitution des ungesättigten Ketocarbonsäure-anions c hat. Die entsprechende Säure konnten wir im Fall des 2,4,6-Trimethyl-*o*-chinolacetats (Ic) und des 2,4-Dimethyl-*o*-chinolacetats (Id) in Substanz erhalten (IIIc und IIId). Die Annahme einer solchen Verschiebung des π-Elektronensystems liefert auch eine Erklärung für das Ausbleiben der Ringspaltung im Fall des Naphthalinderivats (Ie); denn bei diesem Chinol gehört ja die Doppelbindung zwischen C3 und C4 dem aromatischen π-Elektronensystem des anellierten Benzolrings an, kann also an diesem Übergang nicht teilnehmen, so dass hier das Chinol gegen Alkali stabil ist.

Bei den übrigen untersuchten Chinolacetaten ist die Ringspaltung zwar in jedem Fall prinzipiell möglich, doch scheint ihre Geschwindigkeit von den anwesenden Substituenten des Chinols abhängig zu sein. Nur so lässt sich erklären, wieso beim 2,4,6-Trimethyl-*o*-chinolacetat (Ic) eine Isolierung des bei Alkalieinwirkung gebildeten freien *o*-Chinols möglich ist, während bei den übrigen untersuchten Chinolacetaten dessen Isolierung nicht durchgeführt werden konnte, da es unter den Reaktionsbedingungen der Verseifung sofort den weiteren Umsetzungen unterliegt. Worauf die relative Stabilität des 2,4,6-Trimethyl-*o*-chinols (IIc) zurückzuführen ist, lässt sich gegenwärtig nicht entscheiden. Es handelt sich jedenfalls nur um einen graduellen Unterschied gegenüber den anderen *o*-Chinolen, da bei längerer Einwirkung von verdünnten wässrigen Alkalihydroxydlösungen auch hier schon bei Zimmertemperatur eine völlige Aufspaltung des Chinolrings unter Bildung der Säure (IIIc) eintritt, die auch, wie bereits erwähnt, aus Chinolacetat in der Hitze in quantitativer Ausbeute und in der Kälte als Nebenprodukt bei der Alkalieinwirkung erhalten werden konnte. In diesem Zusammenhang ist die Tatsache erwähnenswert, dass auch in der Reihe der *p*-Chinolacetate die 2,4,6-Trimethylverbindung alkalisch zu dem entsprechenden Chinol verseift werden kann,[4] während bei anderen *p*-Chinolacetaten im alkalischen Milieu Produkte sekundärer Umwandlungen erhalten werden.[5]

Der oben vorgeschlagene Reaktionsmechanismus lässt es auch verständlich erscheinen, dass mit den Acetaten acyclischer $\alpha\beta$-ungesättigter α-Ketole, zum Beispiel den Verbindungen:



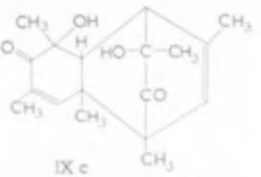
mit Alkali nur Verseifung, aber keine Spaltung der Molekel eintritt.[6]

Vollkommen offen müssen wir die Frage lassen, wieso zwar beim 2,4,6-Trimethyl-*o*-chinolacetat (Ic) und beim 2,4-Dimethyl-*o*-chinolacetat (Id) die ungesättigten Säuren im Reaktionsprodukt aufscheinen, bei der 2-Methyl- und der 2-Phenylverbindung (Ia) und (Ib) jedoch selbst bei Aufarbeitung unter mildesten Bedingungen nur das Lakton erhalten werden konnte. Die Annahme einer Laktonisierung der ungesättigten Säure während der Aufarbeitung scheint bedenklich, da sonst bei ähnlich gebauten $\beta\gamma$-ungesättigten Säuren die entsprechenden Laktone erst beim Erhitzen mit verdünnten Mineralsäuren zugänglich sind.[7] Es ist deshalb auch die

[4] H. Keckeis, Dissertation, Universität Wien, S. 83 (1954).
[5] B. Witkop und S. Goodwin, *Experientia* **8**, 377 (1952); *J. Amer. Chem. Soc.* **79**, 179, (1957).
[6] T. Doeuvre und T. L. Courtois, *Bull. Soc. Chem. Fr.* **11**, 416 (1944).
[7] R. P. Linstead, *J. Chem. Soc.* 115 (1932).

Möglichkeit zur Diskussion zu stellen, dass es bereits vor der endgültigen Ausbildung des Ions c zu einer Anlagerung von Wasser an die Doppelbindung zwischen C3 und C4 kommen kann, wodurch das Ion einer γ-Hydroxysäure gebildet würde, die natürlich wesentlich leichter in das Lakton übergeht. In dem Ätherextrakt der angesäuerten Reaktionsgemische von (Ia) und (Ib) mit Lauge (Hitzeversuch) ist jedenfalls das Lakton bereits vorhanden. Es lässt sich im Fall von (Ib) unmittelbar daraus isolieren; im Fall von (Ia) liefert Methylierung des Ätherextraktes mit Diazomethan nicht den Methylester der ungesättigten Säure, sondern wieder nur das Lakton. Die thermische Beanspruchung bei der Destillation der rohen Reaktionsprodukte kann infolgedessen kaum für die Bildung dieser Laktone verantwortlich gemacht werden.

Wie bereits eingangs erwähnt, kommt es bei der Alkalieinwirkung auf die untersuchten *o*-Chinolacetate neben der Verseifung der Acetylgruppe und der Ringspaltung auch noch zu weiteren Reaktionen, deren Verlauf jedoch weitgehend von der Art der Substitution am Chinolsystem abhängig ist. Ein Teil der so gebildeten Produkte besitzt pro Molekül die doppelte Anzahl an C-Atomen wie das Ausgangschinol. Deren Entstehen muss also auf eine im alkalischen Milieu stattfindende Additions- oder Kondensationsreaktion zurückzuführen sein. So haben wir beim 2,4,6-Trimethyl-*o*-chinolacetat (Ic) bei der Alkalieinwirkung (Zimmertemperatur) neben den bereits erwähnten Stoffen eine Verbindung erhalten, für die wir die Formel $C_{18}H_{24}O_4$ aufstellten. Eine Molgewichtsbestimmung in Campher ergab jedoch nur den halben theoretischen Wert. Der eine von uns (F.W.) erhielt anlässlich eines Zusammen-



IX c

treffens mit Prof. E. Adler (Göteborg) Kenntnis davon, dass von diesem bei der Perjodatoxydation von Mesitol eine Substanz der gleichen Molekularformel und des gleichen Schmelzpunktes erhalten worden war. Die beiden Substanzen erwiesen sich als identisch und Prof. Adler bestätigte durch Versuche, dass die Molekulargewichtsbestimmung in Campher durch Depolymerisation zu tiefe Werte ergab. Prof. Adler und wir fassten den Stoff als Produkt einer Dienaddition des 2,4,6-Trimethyl-*o*-chinolacetats auf und Prof. Adler schlug brieflich[8] eine Formel (IXc) vor, die nach der Konstitutionsaufklärung eines Stoffes, der durch eine Dien-Addition aus 2-Methyl-*o*-chinolacetat entsteht,[9] äusserst wahrscheinlich ist.

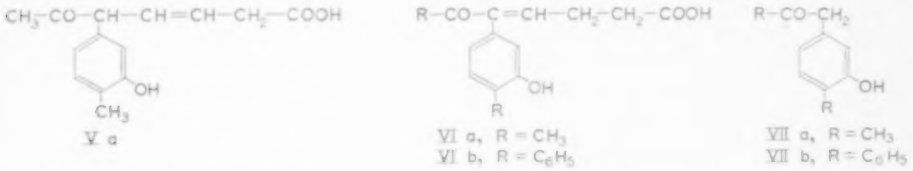
Eine sich ähnlich verhaltende Verbindung (IXd) konnten wir auch bei der Einwirkung von Lauge auf das 2,4-Dimethyl-*o*-chinolacetat (Id) in der Hitze erhalten. Ob es sich hier um die zu (IXc) analoge Verbindung handelt, liess sich noch nicht feststellen.

Eine andere Art von Bildung dimerer Produkte konnten wir beim 2-Methyl-*o*-chinolacetat (Ia) beobachten, wo bei Laugeeinwirkung in der Kälte als einziger identifizierter Stoff eine Säure (Va) erhalten wird, deren Analyse die Summenformel $C_{14}H_{16}O_4$ ergibt. Auch bei Laugeeinwirkung auf (Ia) in der Hitze lässt sich neben dem

[8] E. Adler, 31.8.1955.
[9] W. Metlesics und F. Wessely, *Mh. Chem.* **88**, 108 (1957).

Lakton (IVa) in etwa gleicher Gewichtsmenge wie dieses eine kristallisierte Säure (VIa) isolieren. Sie besitzt dieselbe Summenformel wie (Va), unterscheidet sich jedoch durch den Schmelzpunkt und liefert auch eine eindeutige Mischschmelzpunktsdepression. Die Art der Isomerie der beiden Verbindungen wird aus der Tatsache ersichtlich, dass beide Säuren bei der katalytischen Hydrierung mit Pd-Katalysator ein Mol. Wasserstoff aufnehmen und hierbei in dasselbe Dihydroprodukt übergehen. Es ist also in beiden Säuren die Anwesenheit einer C=C-Doppelbindung anzunehmen und sie unterscheiden sich entweder durch Ortsisomerie dieser Doppelbindung oder sind als geometrische Isomere anzusprechen. Das IR-Spektrum weist auf eine verschiedene Lage der Doppelbindung hin. Dieser Befund wird auch durch die Ergebnisse der Ozonisierung gestützt; denn bei der Säure (Va) findet man unter den Ozonisierungsprodukten Malonsäure, während bei der Säure (VIa) Bernsteinsäure und 3-Hydroxy-4-methyl-benzoesäure nachgewiesen werden konnte.

Beide Säuren besitzen neben der Carboxylgruppe auch eine Ketogruppe, die durch die Bildung eines Dinitrophenylhydrazons, und eine phenolische Hydroxygruppe, die durch eine Zerewitinoffbestimmung nachgewiesen wurde. Die C-Methylbestimmung nach Kuhn–Roth liefert 2 Mol. Essigsäure. Besonders bemerkenswert ist aber die Tatsache, dass beim Erhitzen mit 2N NaOH die Säure (VIa) eine hydrolytische Aufspaltung unter Bildung eines Ketophenols $C_{10}H_{12}O_2$ erleidet, dem nach einer eindeutigen Synthese, über die an anderer Stelle berichtet wurde,[10] die Konstitution (VIIa) zukommt.



V a

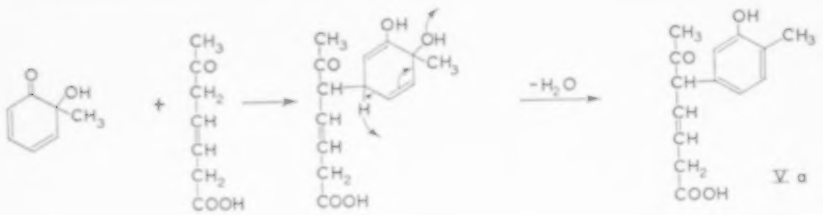
VI a, R = CH_3
VI b, R = C_6H_5

VII a, R = CH_3
VII b, R = C_6H_5

Alle diese angeführten Eigenschaften lassen darauf schliessen, dass es sich bei der, bei Behandlung von (Ia) in der Siedehitze gebildeten Säure um die 5-(3-Hydroxy-4-methyl-phenyl)-hepten-(4)-on-(6)-säure (VIa) handelt. Für die Struktur der bei der analogen Reaktion bei Zimmertemperatur entstehenden Säure (Va) ergibt sich die Formel einer 5-(3-Hydroxy-4-methyl-phenyl)-hepten-(3)-on-(6)-säure. Die Lage der Doppelbindung in dieser Säure ergibt sich aus dem erwähnten Ozonisierungsergebnis, sowie aus dem Befund, dass nach dem IR-Spektrum die C=C-Doppelbindung weder mit der Ketogruppe, noch mit der Carboxylgruppe konjugiert sein kann, was nur bei ihrer Stellung zwischen C3 und C4 der Fall ist.

Im Hinblick auf eine Erklärung der Bildung dieser beiden Säuren muss die Tatsache berücksichtigt werden, dass die Säure (Va) bei der Behandlung mit siedender 0,2N Natronlauge glatt in die Säure (VIa) übergeht. Es ist also (Va) als primäres Reaktionsprodukt aufzufassen, das bei der Durchführung des Versuchs in der Hitze in weiterer Reaktion (VIa) bildet. Die primär entstehende Säure (Va) jedoch kann als Produkt einer 1:4-Addition des Ions c der ungesättigten Säure an das C=C—C=O-Doppelbindungssystem von unverändertem Chinol gedeutet werden, da ja das Ion c in C5 eine durch die benachbarte Doppelbindung und die benachbarte Ketogruppe aktivierte Methylengruppe besitzt. Die Durchführbarkeit solcher "Michael-Additionen" an Chinolacetaten wurde im Rahmen einer anderen an unserem Institut

durchgeführten Arbeit[10] gezeigt. Dort wurde auch eine Synthese des Dihydroproduktes der beiden Säuren (Va) und (VIa) beschrieben, wodurch deren Konstitution weiter gesichert erscheint.



Die Ursache für die Umlagerung von (Va) in (VIa) ist wohl in der energetischen Begünstigung von (VIa) durch die Konjugation wischen C=C- und C=O-Doppelbindung zu suchen. Bei der Einwirkung von stärkerem Alkali kommt es dann zu einer hydrolytischen Aufspaltung dieser C=C-Doppelbindung, wodurch das Ketophenol (VIIa) gebildet wird.

Dass bei der Einwirkung des kalten Alkalis auf (Ia) kein Lakton (IVa), sondern nur die Säure (Va) gebildet wird, ist verständlich, wenn die Geschwindigkeit der Ringspaltung in der Kälte kleiner ist, als die der Addition des dadurch entstandenen Spaltungsproduktes an noch unverändertes Chinolsystem. Wenn die Ringspaltung mit der gleichen Geschwindigkeit abläuft wie die Michael-Addition, dann muss man rund 50% des monomeren Stabilisierungsproduktes der Ringspaltungsreaktion, nämlich das Lakton (IVa) erwarten, so wie es bei 100° der Fall ist.

Beim Zufügen einer alkoholischen Lösung von 2-Phenyl-*o*-chinolacetat (Ib) zu siedender 0,2 N wässriger Natronlauge erhält man neben Acetophenon, über dessen Bildungsweise noch zu sprechen sein wird, in wechselnden Mengen ein kristallisiertes Produkt (VIIb) vom Schmp. 149–151° mit der Summenformel $C_{20}H_{16}O_2$, das ein phenolisches Hydroxyl und eine Ketogruppe aufweist, wie aus der Bildung eines Acetylderivats, bzw. eines Dinitrophenylhydrazons hervorgeht. Wir vermuteten nun hier eine Analogie zu dem Ketophenol (VIIa), das bei der hydrolytischen Spaltung von der aus 2-Methyl-*o*-chinolacetat (Ia) gebildeten Säure (VIa) erhalten wird. Die auf Grund dieser Annahme für (VIIb) angenommene Konstitution eines (3-Hydroxy-4-phenyl)-benzyl-phenyl-ketons konnte tatsächlich durch Synthese dieses Ketophenols bewiesen verden.[10]

Im Hinblick auf diesen Befund liegt die Annahme nahe, dass auch aus (Ib) durch eine 1:4-Anlagerung von primärem Spaltungsprodukt (IIIb) an das C=C—C=O-Doppelbindungssystem des Chinols eine der Säuren (Va) oder (VIa) analoge Verbindung gebildet wird, in der sich aber die Anwesenheit einer Phenylgruppe durch eine, gegenüber der entsprechenden Methylverbindung wesentlich erleichterte hydrolytische Spaltbarkeit der C=C-Doppelbindung auswirkt, so dass unter den angewandten experimentellen Bedingungen nicht die entsprechende Säure selbst, sondern nur ihr Spaltungsprodukt gefunden werden kann.

Um diese vermutete dimere Säure (VIb) selbst zu erhalten, liessen wir zu einer Dioxanlösung von (Ib) bei Zimmertemperatur tropfenweise wässrige 2N NaOH zufliessen, arbeiteten also unter Bedingungen, die während der Reaktion keinen lokalen

[10] F. Langer und F. Wessely, *Mh. Chem.* **88**, 298 (1957).

Überschuss von Lauge aufkommen lassen und so einerseits einer Dimerisation förderlich sein, und anderseits die weitere Spaltung der dimeren Säure verhindern sollten. Wir erhielten so tatsächlich ein über 250° im Hochvakuum übergehendes, hochviskoses Öl, das bei der acidimetrischen Titration Werte lieferte, die die Annahme der Anwesenheit der erwünschten Säure rechtfertigten; Versuche jedoch, aus dieser harzähnlichen Masse eine reine, kristallisierte Verbindung zu erhalten, blieben erfolglos. Durch Behandlung dieses Produktes mit Diazoäthan erhielten wir jedoch hieraus eine kristallisierte Verbindung der Summenformel $C_{26}H_{24}O_4$, die als Äthylester der Säure (VIb) anzusprechen war. Es liegt also tatsächlich in diesem Produkt eine dimere Säure vor, deren Reindarstellung und Isolierung aber bisher nicht gelungen ist.

Überraschend ist die Beobachtung, dass der Äthylester von (VIb) auch unmittelbar aus (Ib) erhalten werden kann, wenn dieses in äthanolischer Lösung tropfenweise mit 2N wässriger NaOH bei Zimmertemperatur versetzt wird. Der so erhaltene Ester wird—wie nach den oben erwähnten Verhältnissen zu erwarten ist—mit Lauge beim Erwärmen rasch gespalten, wobei als Spaltprodukt das Ketophenol (VIIb) gebildet wird, dessen Bildung gleichzeitig einen wesentlichen Beitrag zur Konstitutionsbestimmung dieses Esters lieferte. Dass die Spaltung an der C=C-Doppelbindung einsetzt, geht aus der Tatsache hervor, dass das Hydrierungsprodukt dieses Esters—nach Aufnahme von 2 Mol. Wasserstoff—ohne Schwierigkeit zu einer Säure verseift werden kann, ohne dass eine Spaltung zu beobachten ist. Die Lage dieser C=C-Doppelbindung ist auf Grund des IR-Spektrums in Konjugation zur C=O-Doppelbindung anzunehmen, entspricht also der Doppelbindung in der Säure (VIa).

Die Frage, in welcher Stufe des Reaktionsablaufes bei der Einwirkung von Lauge auf (Ib) in alkoholischer Lösung diese Estergruppierung gebildet wird, muss noch offen bleiben; eine sekundäre Äthylierung einer primär gebildeten Carboxylgruppe scheint jedenfalls unter den angewandten Bedingungen als völlig ausgeschlossen gelten zu können. Am ehesten dürfte noch die Annahme gerechtfertigt sein, dass die Chinolacetate in alkoholischer Lösung Alkohol an die Ketogruppe unter Bildung einer Halbacetalform anlagern—worauf auch spektroskopische Befunde hinweisen—, sodass also bereits von vornherein in diesem Milieu die Äthoxygruppe an dem C-Atom sitzt, das im Lauf des Reaktionsgeschehens zur Carboxylgruppe wird. Wir konnten übrigens auch beim 2-Methyl-*o*-chinolacetat (Ia) unter analogen Bedingungen einen—hier allerdings flüssigen—Äthylester erhalten, der nach den Ergebnissen der IR-Spektroskopie allerdings eine unkonjugierte C=C-Doppelbindung besitzt, also als Äthylester der Säure (Va) anzusprechen ist.

Beim 2,4,6-Trimethyl-*o*-chinolacetat (Ic) ist es uns nicht gelungen, bei der Alkalieinwirkung ein der Michael-Addition entsprechendes dimeres Produkt aufzufinden. Hier kommt es an Stelle dessen zu der bereits erwähnten Dien-Addition.

In Analogie zu der Tatsache, dass die dimere Säure (VIb) durch die Anwesenheit der Phenylgruppe zu einer leichteren hydrolytischen Spaltung neigt als die entsprechende Methylverbindung (VIa) steht auch der bereits erwähnte Befund, dass das aus (Ib) in der Kälte erhältliche Lakton (IVb) beim Behandeln mit Lauge in der Hitze eine hydrolytische Spaltung unter Bildung von Acetophenon erleidet. Aus dieser Tatsache wird auch die Bildung des Acetophenons beim Behandeln von (Ib) mit siedender Natronlauge verständlich. Ähnliche Spaltungen sind auch bereits in der Literatur beschrieben worden.[11] Im Fall des aus (Ia) erhaltenen Laktons (IVa)

[11] A. v. Wacek und E. David, *Ber. Dtsch. Chem. Ges.* **70**, 190 (1937).

konnte sie zwar von uns nicht beobachtet werden, doch läuft die erwähnte Bildung von Dianisalaceton bei der alkalischen Kondensation des Laktons (IVa) mit Anisaldehyd auf eine analoge Spaltung hinaus.

Abschliessend sei noch festgestellt, dass die bisher beschriebenen Reaktionsstufen bei der Einwirkung von Alkalihydroxyd auf *o*-Chinolacetate, die in Abb. 1 zur Übersicht zusammengestellt sind, sicherlich noch von weiteren Vorgängen begleitet werden, da bei den meisten durchgeführten Versuchen ausser den isolierten und identifizierten Produkten auch wechselnde, doch meist geringe Mengen noch ungeklärter Nebenprodukte gebildet wurden.

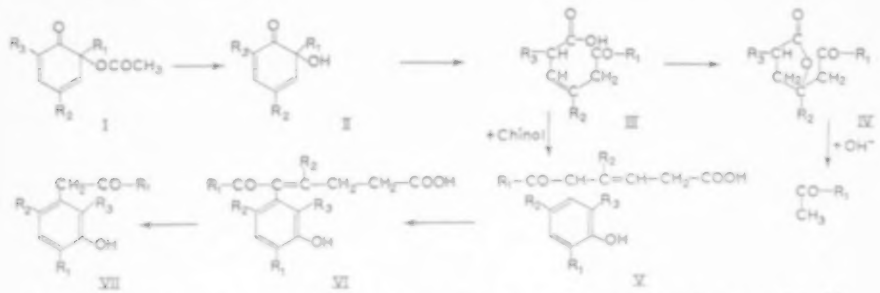


ABB. 1. Die Art der Substituenten R_1, R_2, R_3 entspricht der in den Chinolacetaten (Ie)–(Id).

EXPERIMENTELLER TEIL

Durchführung der Alkalieinwirkung auf o-*Chinolacetate*

2-*Methyl*-o-*chinolacetat* (Ia). Die *quantitative Bestimmung* des Alkaliverbrauchs von (Ia) durch Zusatz von überschüssiger 0,2N NaOH zu einer Lösung des Chinolacetats und Rücktitration des Laugenüberschusses ergab nach 10 Minuten einen Endwert von 1,9 Mol. NaOH auf 1 Mol. (Ia) in der Siedehitze und 1,5 Mol. NaOH auf 1 Mol. (Ia) bei Zimmertemperatur.

Zur *präparativen Isolierung* der bei *Laugeeinwirkung bei Zimmertemperatur* gebildeten Produkte verfuhren wir folgendermassen: 8,4 g (50 mMol.) (Ia) wurden in 450 ml Wasser unter Erwärmen gelöst. Die wieder auf Zimmertemperatur abgekühlte Lösung befreiten wir durch Einleiten von Stickstoff von gelöstem Sauerstoff und fügten unter weiterem Stickstoff-Einleiten im Lauf von 15 Minuten tropfenweise 50 ml 2N NaOH (100 mMol.) zu. Die beim Zufügen der ersten Laugetropfen auftretende starke Verfärbung nach rotbraun ging bei weiterem Laugezusatz wieder zurück, so dass eine goldgelbe Lösung resultierte. Diese liessen wir weitere 15 Minuten unter N_2-Strom stehen und sättigten sie hierauf mit CO_2. Der so erhaltenen bikarbonatalkalischen Lösung konnten wir mit Äther nur geringfügige Mengen eines schwerflüchtigen, nicht kristallisierenden Produktes entziehen, auf dessen weitere Untersuchung wir nicht eingingen. Die wässrige Lösung wurde hierauf mit HCl angesäuert und mit Äther extrahiert. Der Rückstand des Ätherextraktes bildete ein gelbes Öl (7,5 g), aus dem durch Erhitzen bei 10 Torr am Wasserbad etwa 2 g Essigsäure abdestilliert werden konnten. Hierauf erstarrte beim Erkalten der Rückstand zu einer harten Kristallmasse, aus der durch—allerdings sehr verlustreiches—mehrmaliges Umkristallisieren aus Methanol–Wasser schliesslich fast *farblose Kristalle von* (Va) erhalten werden konnten, die bei 123° schmolzen und

in Methanol, Äthanol, Aceton und Äther gut, hingegen in Wasser und Petroläther schlecht löslich sind ($C_{14}H_{16}O_4$: Ber. C, 67,73; H, 6,50; akt. H,0,81; Äquiv. Gew., 248. Gef. C, 67,87; H, 6,57; akt. H, 0,72; Äquiv. Gew., 255).

Die *Einwirkung von Lauge auf* (Ia) *bei Siedehitze* wurde unter sonst völlig analogen Reaktionsbedingungen wie oben durchgeführt. Auch hier kam es zu den erwähnten Farberscheinungen. Die Ätherextraktion der nach Abkühlen des Reaktionsgemisches und Sättigung mit CO_2 erhalten bicarbonatalkalischen Lösung lieferte wieder nur einige Zehntelgramme eines zähen, nicht kristallisierenden Öls, auf dessen weitere Untersuchung wir verzichteten. Durch Ätherextraktion der anschliessend mit HCl angesäuerten wässrigen Lösung erhielten wir 8 g eines rotbraunen Öls, von dem bei 10 Torr 2 g Essigsäure abdestilliert werden konnten. Der Rückstand wurde dann zunächst im Kugelrohr bei 0,2 Torr destilliert. Hierbei erhielten wir als erste Fraktion bei 120–160° Badtemperatur 2,5 g einer hellgelben Flüssigkeit und als zweite Fraktion bei 200–220° 2,5 g eines sehr zähen Öls, das beim Behandeln mit Äther–Petroläther fast vollkommen durchkristallisierte.

Die erste, ölige Fraktion wurde zur weiteren Reinigung in einem Widmer-Kolben bei 0,2 Torr destilliert, wobei bei einer Temperatur von 110–115° das *Lakton* (IVa) *als farbloses Öl* mit $n_D^{20} = 1{,}4620$ überging ($C_7H_{10}O_3$: Ber. C, 59,14; H, 7,09; Äquiv. Gew., 142. Gef. C, 59,40; H, 7,33; Äquiv. Gew., 148).

Die kristallisierende zweite Fraktion wurde mehrmals aus Methanol–Wasser umkristallisiert, wodurch wir 2 g *der Säure* (VIa) vom Schmp. 136–140° erhielten. Das Löslichkeitsverhalten dieser Säure war analog wie das von (Va) ($C_{14}H_{16}O_4$: Ber. C, 67,73; H, 6,50; Äquiv. Gew., 248. Gef. C, 67,56; H, 6,40; Äquiv. Gew., 258).

Neben (VIa) konnten wir bei einzelnen Ansätzen in der zweiten Fraktion auch noch eine geringe Menge einer in Äther schwerer löslichen Substanz erhalten, die nach Umkristallisieren aus Äther–Petroläther einen Schmp. von 170–174° zeigte. Eine weitere Untersuchung dieser Substanz wurde nicht durchgeführt. Es könnte sich hierbei um das der Säure (VIa) entsprechende Lakton handeln ($C_{14}H_{16}O_4$: Ber. C, 67,73; H, 6,50. Gef. C, 67,74; H, 6,17).

Um *eventuell* im Reaktionsgemisch vorliegende, dem Lakton (IVa) entsprechende *β,γ-ungesättigte Säure nachzuweisen*, wurde bei einem Versuch der Ätherextrakt der angesäuerten Lösung nicht destilliert, sondern mit einem Überschuss einer ätherischen Diazomethanlösung methyliert. Die Ätherlösung entsäuerten wir hierauf mit $NaHCO_3$-Lösung. Der Rückstand des Äthers wurde im Kugelrohr destilliert. Es ging jedoch bei der für den zu erwartenden Ester entsprechenden Temperatur nur eine sehr geringe Menge eines nicht näher untersuchten Öls über. Die Hauptmenge dieses Rückstands erwies sich als der bei 180–200° übergehende Methylester der Säure (VIa). Aus der erwähnten $NaHCO_3$-Lösung konnte durch die oben beschriebene Aufarbeitung das Lakton (IVa) in üblicher Ausbeute erhalten werden.

Unter analogen Bedingungen liessen wir auf 3,5 g (Ia) *in äthanolischer Lösung NaOH bei Zimmertemperatur* einwirken. Nach Verdünnen des Reaktionsgemisches mit Wasser liessen sich daraus durch Ätherextraktion 1,2 g eines gelbbraunen Öls gewinnen, das bei der Destillation im Kugelrohr zwei Fraktionen ergab:

(1) 95–130°/0,05 Torr: 0,5 g eines farblosen Öls,

(2) 165–175°/0,05 Torr: 0,6 g eines zähen, gelben Öls.

Bei der Äquivalentgewichtsbestimmung zeigten beide Fraktionen nur einen sehr

geringen direkten Alkaliverbrauch in der Kälte. Die durch Behandeln mit überschüssiger Natronlauge bei 90° und Rücktitration des Laugeüberschusses ermittelten Werte lagen mit 222, bzw. 326 höher als die für die reinen Äthylester der Säuren (IIIa) und (VIa) zu erwartenden Werte (170, bzw. 276). Die zweite Fraktion lieferte nach Behandeln mit der äquivalenten Laugemenge bei 90° nach entsprechernder Aufarbeitung Kristalle, die sich mit der Säure (VIa) identisch erwiesen, wodurch sich die Annahme der Anwesenheit des entsprechenden Esters in dieser Fraktion rechtfertigt.

2-*Phenyl*-o-*chinolacetat* (Ib). Zu einem Gemisch von 25 ml 2N NaOH und 25 ml Methanol wurde bei *Zimmertemperatur* im Laufe von 30 Minuten unter Stickstoffstrom tropfenweise eine Lösung von 5 g (Ib) in 40 ml Dioxan zugesetzt. Sowohl das alkalische dunkelrot gefärbte Reaktionsgemisch, als auch die mit CO_2 anschliessend gesättigte Lösung lieferten bei der Ätherextraktion nur sehr geringe Mengen zäher, öliger Substanzen, die nicht näher untersucht wurden. Nach dem Ansäuern der Reaktionslösung mit HCl erhielten wir durch Ätherextraktion 3,5 g eines Öls, das nach mehrfacher Destillation im Kugelrohr (140–170° 0,4 Torr) ein rasch erstarrendes Destillat ergab, aus dem wir durch Umkristallisieren aus Aceton–Petroläther schliesslich 0,8 g weisser, bei 122–124° schmelzender *Kristalle von* (IVb) erhielten ($C_{12}H_{12}O_3$: Ber. C, 70,57; H, 5,92; Äquiv. Gew., 204; Mol-Gew., 204. Gef. C, 70,43; H, 5,91; Äquiv. Gew., 202; Mol-Gew., (Rast) 208).

Die *Einwirkung von Lauge auf* (Ib) *in der Siedehitze* haben wir so durchgeführt, dass unter Stickstoff zu 500 ml 0,1N NaOH 4,6 g (Ib) zugefügt und 30 Minuten lang zum Sieden erhitzt wurde. Das hierbei über einen Kühler abdestillierende Wasser wurde aus einem Tropftrichter laufend ergänzt. Das *Destillat* enthielt neben Wasser noch *Acetophenon*, das durch Ätherextraktion und Destillation isoliert wurde. Sein Nachweis erfolgte durch Bildung des bei 234° schmelzenden Dinitrophenylhydrazons und des bei 54–55° schmelzenden Oxims. Beide Derivate waren mit authentischen Proben identisch.

Die oben erhaltene alkalische Lösung sättigten wir mit CO_2, worauf sich nach einiger Zeit ein kristalliner Niederschlag abschied, der abfiltriert und durch Umkristallisieren aus Äther–Petroläther gereinigt wurde. Die so gebildeten *farblosen Nadeln des Ketophenols* (VIIb) schmolzen bei 149–151° ($C_{20}H_{16}O_2$: Ber. C, 83,34; H, 5,60. Gef. C, 83,26; H, 5,67).

Die mit CO_2 gesättigte Lösung des Reaktionsgemisches säuerten wir schliesslich noch mit HCl an. Es konnten hieraus jedoch durch Ätherextraktion nur braune amorphe, undestillierbare Massen gewonnen werden.

Zur *Gewinnung dimerer Produkte* wurden 4,6 g des Chinolacetats (Ib) in 50 ml Dioxan gelöst und mit 20 ml 2N NaOH bei Zimmertemperatur geschüttelt. Es trat hierbei nach einigen Minuten Lösung unter Erwärmen und Rotbraunfärbung ein. Das Reaktionsgemisch wurde hierauf mit Wasser verdünnt und mit Äther extrahiert. Sowohl dieser Ätherextrakt als auch der nach Sättigung des Reaktionsgemisches mit CO_2 erhaltene lieferten jeweils einen nur ganz geringfügigen nicht weiter untersuchten Rückstand. Nach Ansäuern der wässrigen Lösung mit HCl erhielten wir durch Ätherextraktion 3 g eines gelbbraunen, zähen Öls, das sich nicht zur Kristallisation bringen liess. Die Kugelrohrdestillation bei 250°/0,02 Torr ergab ein gelb-Gaunes Glas, dessen Laugeverbrauch bei der Äquiv. Gew.-Titration (Ber. 372; bref. 368) die Annahme der Anwesenheit der *Säure* (VIb) rechtfertigte.

1,4 g der erhaltenen Säure wurden in Äther gelöst und unter Eiskühlung mit einem Überschuss ätherischer Diazoäthanlösung versetzt. Hierbei erhielten wir nach Abdestillieren des Äthers einen braunen, zähen Rückstand, der durch Kugelrohrdestillation (195–220°/0,06 Torr) 1 g eines braunen Öls ergab, aus dem wir durch mehrfaches Umlösen aus Benzol unter Zusatz von Tierkohle 0,25 g weißer Kristalle des *Esters* mit dem Schmp. 150,5–152° erhielten, die mit dem nach der unten beschriebenen Methode direkt aus Chinolacetat erhaltenen Ester identisch waren.

Zur *direkten Darstellung des Esters der Säure* (VIb) aus (Ib) wurden 4,6 g des Chinolacetats in 160 ml Äthanol gelöst und bei Zimmertemperatur langsam 20 ml 2N NaOH zugefügt. Beim Verdünnen des Reaktionsgemisches mit Wasser trat eine starke Trübung auf. Durch Ausäthern dieses Gemisches wurden 3 g einer braunen öligen Substanz gewonnen, die bei der Kugelrohrdestillation ausser einer geringen Menge unumgesetztem Chinolacetat ein bei 190–220°/0,2 Torr übergehendes braunes Öl lieferte, das allmählich kristallisierte. Durch mehrfaches Umkristallisieren aus Benzol–Petroläther unter Zusatz von Tierkohle erhielten wir weisse Kristalle des Esters vom Schmp. 150–152° ($C_{28}H_{24}O_4$: Ber. C, 77,98; H, 6,04; OC_2H_5, 11,3; Äquiv. Gew., 400. Gef. C, 78,22; H, 6,06; OC_2H_5, 12,5; Äquiv. Gew., 389).

Durch Ansäuern der obigen wässrigen Lösung konnten nur etwa 1 g undestillierbarer Produkte erhalten werden, die nicht weiter untersucht wurden.

2,4,6-*Trimethyl*-o-*chinolacetat* (Ic). 5 g des Chinolacetats (Ic) wurden in 30 ml Äthanol gelöst und tropfenweise bei *Zimmertemperatur* unter Stickstoffstrom zu einer Mischung von 30 ml 2N NaOH und 220 ml Wasser im Lauf von 30 Minuten zufliessen gelassen. Das sich gelb färbende Reaktionsgemisch ätherten wir anschliessend sofort mehrmals aus. Nach Abdestillieren des Äthers hinterblieben 2,5 g eines gelben Öls, das durch Destillation im Kugelrohr in zwei Fraktionen zerlegt werden konnte:

(1) 75–80°/0,1 Torr: 0,9 g eines gelben Öls,

(2) Rückstand: gelbe Kristalle.

Die leichtflüchtige Fraktion wurde aus einem Widmerkolben nochmals destilliert (80–85°/0,2 Torr), wodurch kristallisierendes *Chinol* (IIc) erhalten wurde, das nach Umkristallisieren aus Petroläther bei 37–39° schmolz, ($C_9H_{12}O_2$: Ber. C, 71,02; H, 7,95. Gef. C, 70,81; H, 7,67).

Der kristallisierende Rückstand wurde aus Petroläther–Äther umgelöst und ergab farblose Kristalle der *dimeren Substanz* (IXc), die bei 181–182° schmolzen und mit einer von Prof. Dr. E. Adler freundlicherweise überlassenen Probe identisch waren ($C_{18}H_{24}O_4$: Ber. C, 71,02; H, 7,95; akt. H, 0,60. Gef. C, 71,50; H, 8,07; akt. H, 8,07).

Nach Ansäuern der oben beschriebenen ausgeätherten Lösung konnten durch weitere Ätherextraktion noch 1,2 g eines gelben Öls erhalten werden, das bei der Kugelrohrdestillation ein schwach gelbliches Destillat ergab (90–100°/0,05 Torr), dem auf Grund seines Äquivalentgewichtes, sowie seiner weiter unten beschriebenen Eigenschaften die Struktur der *Säure* (IIIc) zugeordnet wurde, wenn auch die Analyse —anscheinend wegen nicht genügender Reinheit des hygroskopischen Präparats—nur schlecht mit den berechneten Werten im Einklang stand ($C_9H_{14}O_3$: Ber. C, 63,51; H, 8,29; Äquiv. Gew., 170. Gef. C, 62,47; H, 8,47; Äquiv. Gew., 171).

Bei der Umsetzung mit Semicarbazid ergab diese Säure ein kristallisiertes,

farbloses *Semicarbazon*, das nach Umkristallisieren aus Methanol–Wasser bei 157–162° schmolz ($C_{10}H_{17}N_3O_3$: Ber. C, 52,85; H, 7,54; N, 18,49. Gef. C, 52,59; H, 7,55; H, 18,46).

Die *Einwirkung von Lauge auf* (Ic) *bei Siedehitze* erfolgte in der Weise, dass wir 5,5 g (Ic) in 50 ml Äthanol gelöst im Lauf von 15 Minuten zu einer Mischung von 30 ml 2N NaOH und 220 ml H_2O unter Stickstoffstrom zufliessen liessen. Nach weiteren 5 Minuten Kochen wurde unter Einleiten von CO_2 auf Zimmertemperatur abgekühlt. Diese Lösung lieferte bei der Ätherextraktion nur 0,7 g eines nicht näher untersuchten Öls.

Nach Ansäuern der wässrigen Lösung mit HCl konnte durch Ätherextraktion 4,0 g eines orange-gelben Öls gewonnen werden, das im Kugelrohr bei 80–120°/0,06 Torr nahezu rückstandfrei destillierte und dabei die *Säure* (IIIc) in Form eines farblosen Öls lieferte.

2,4-*Dimethyl*-o-*chinolacetat* (Id). 3,6 g (Id) wurden in 20 ml Äthanol gelöst und im Verlauf von 15 Minuten unter Stickstoffstrom bei *Zimmertemperatur* uz einer Mischung von 20 ml 2N NaOH und 380 ml Wasser zufliessen gelassen. Die sich rötlich verfärbende Lösung ätherten wir nach 1 Stunde Stehen mehrmals aus. Dieser Ätherextrakt enthielt 0,9 g eines gelben Öls, das bei der Kugelrohrdestillation neben unumgesetztem Chinolacetat ein nichtkristallisierendes Produkt lieferte, das wir nicht weiter untersuchten.

Nach der Sättigung der wässrigen Lösung mit CO_2 wurden durch Ätherextraktion 0,15 g eines rotbraunen Öls erhalten, das wir ebenfalls nicht untersuchten.

Die angesäuerte Lösung lieferte bei der Ätherextraktion 1,6 g eines Öls, aus dem durch Kugelrohrdestillation bei 100–130°/0,05 Torr 1,3 g öliges Destillat erhalten wurden, dem wir auf Grund der Äquivalentgewichtsbestimmung (Ber. 156; Gef. 155) und der Bildung des unten angeführten Semicarbazons die Struktur der *Säure* (IIId) zuordneten.

Das aus dieser Säure in der üblichen Weise hergestellte *Semicarbazon* schmolz nach Umkristallisieren aus Wasser bei 168–171,5° ($C_9H_{15}N_3O_3$: Ber. C, 50,69; H, 7,09; N, 19,71; Äquiv. Gew., 213. Gef. C, 50,56; H, 7,28; N, 19,20; Äquiv. Gew., 216).

Nach der *Umsetzung* von 3,6 g (Id) in 20 ml Äthanol mit 200 ml 0,2 N NaOH *bei Siedehitze* unter den üblichen Bedingungen konnten aus der alkalischen Lösung durch Ätherextraktion 0,5 g eines gelben Öls isoliert werden, das beim Stehen über Nacht kristallisierte. Die Kugelrohrdestillation ergab ein rasch zu weissen Kristallen erstarrendes Destillat. Die so gebildeten *Kristalle* des Dimeren (Xd) schmolzen nach Umkristallisieren aus Benzol bei 126–127° ($C_{16}H_{20}O_4$: Ber. C, 69,54; H, 7,30. Gef. C, 69,94; H, 7,10).

Aus der mit CO_2 gesättigten Lösung konnte keine Substanz durch Ausäthern gewonnen werden.

Die mit HCl angesäuerte Lösung lieferte 2,5 g eines Produktes, das im Kugelrohr destilliert bei 100–140°/0,05 Torr 2,2 g eines schwach gelben Öls ergab, in dem nach den Ergebnissen der Äquivalentgewichtsbestimmung neben der *Säure* (IIId) noch etwa 25% des entsprechenden Laktons anzunehmen waren.

2-*Methyl*-3:4-*benzo*-o-*chinolacetat* (Ie). Zur Darstellung des Chinolacetats liessen wir das nach Bargellini und Silvestri[12] dargestellte entsprechende Chinol

[12] G. Bargellini und S. Silvestri, *Ganz. Chim. Ital.* **37**, 413 (1907).

VOL. 4 1958

16 Stunden mit Essigsäureanhydrid und etwas absolutem Pyridin bei Zimmertemperatur stehen. Nach dem Abdampfen des Lösungsmittels im Vakuum kam der Rückstand zur Kristallisation. Er wurde aus Benzol umgelöst und bildet lange Nadeln vom Schmp. 128°.

0,06 g dieses Chinolacetats (Ie) wurden in 10 ml Äthanol und 25 ml Wasser gelöst und mit 15 ml 1N NaOH versetzt. Die Titration des Laugeüberschusses ergab selbst nach 2 Stunden einen Verbrauch, der den für die Verseifung des Acetoxylrestes nicht überstieg. Aus der alkalischen Lösung konnte ein Produkt isoliert werden, das aus Wasser umkristallisiert von 86–88° schmolz und mit dem freien Chinol keine Depression des Schmelzpunktes ergab.

Untersuchung der Reaktionsprodukte

Lakton der 4-Hydroxy-heptanon-(6)-säure(IVa). Zur *Darstellung des Semicarbazons* wurde in der üblichen Weise verfahren. Das aus Wasser umkristallisierte Reaktionsprodukt schmolz bei 172–174°. Es ist in heissem Wasser gut, in Alkohol und Äther schlecht löslich ($C_8H_{13}N_3O_3$: Ber. C, 48,23; H, 6,58; N, 21,10. Gef. C, 48,18; H, 7,03; N, 20,88).

Zur *Umsetzung mit Anisaldehyd* wurden 0,5 g des Laktons mit 0,5 g Anisaldehyd in 20 ml 2N NaOH 6 h bei Zimmertemperatur geschüttelt. Aus der sich stark braun färbenden Lösung schieden sich gelbe Kristalle ab, die aus Methanol umkristallisiert bei 130–132° schmolzen und mit einem authentischen Präparat von *Dianisalaceton* keine Schmelzpunktsdepression zeigten.

Zur *Oxydation von* (IVa) *mit* $KMnO_4$ wurden 1,2 g des Laktons in 50 ml 1 N NaOH gelöst und solange in der Kälte mit 2% iger $KMnO_4$-Lösung versetzt, bis die violette Farbe bestehen blieb. Nach Zusatz von 2 g Natriumsulfit säuerten wir mit Schwefelsäure an. Die klare Lösung wurde mit Äther extrahiert und der Abdampfrückstand des Ätherextraktes einer Wasserdampfdestillation unterworfen. Das wässrige Destillat wurde nach der Neutralisation mit verdünnter NaOH zur Trockene eingedampft und ergab nach neuerlichem Ansäuern mit 0,1N H_2SO_4 mit S-Benzylthiuroniumchlorid eine Substanz vom Schmelzpunkt 134–136°, die sich mit dem *Benzylthiuroniumsalz der Essigsäure* als identisch erwies.

Die *nicht wasserdampfflüchtigen Oxydationsprodukte* wurden der wässrigen Lösung mit Äther entzogen. Die Sublimation des Rückstandes der Ätherlösung bei 120–130°/0,1 Torr ergab in guter Ausbeute eine bei 180–182° schmelzende Substanz, die als *Bernsteinsäure* identifiziert wurde.

Zur Synthese von (IVa) wurden zunächst 5 g 4-Oxobuttersäure-äthyl-ester[13] und 8 g Bromessigsäureäthylester in 200 ml Äther–Benzol-Gemisch gelöst zu 50 g Zinkgriess unter Rühren langsam zufliessen gelassen und dann 2 Stunden unter Rückfluss erhitzt. Nach Hydrolyse mit kaltem Wasser und Zugabe von verdünnter Schwefelsäure bis zur Lösung des Zinkhydroxydes wurde ausgeäthert. Der Rückstand der ätherischen Lösung lieferte bei der Destillation (130–140°/0,2 Torr) 5,5 g eines schwach gelben Öls, das durch Kochen mit 35 ml 2 N NaOH verseift wurde. Die so gewonnene 3-Hydroxy-adipinsäure führten wir dann durch Erhitzen mit 50% iger Schwefelsäure in das Lakton über.

[13] W. Wislicenus, E. Böklen und F. Deuthe, *Liebigs. Ann.* **363**, 347 (1908); S. Sugasawa, *J. Pharm. Soc., Japan* **534**, 64 (1926).

Die Überführung in das Chlorid des 3-Hydroxy-adipinsäure-laktons gelang nur mit einer sehr schlechten Ausbeute. 25,5 g des Laktons wurden mit 50 ml absolutem Benzol vermischt und unter Zusatz von 15 ml Thionylchlorid in 35 ml absolutem Benzol unter Rückfluss bis zur Beendigung der HCl-Entwicklung erhitzt. Nach Abdestillieren des Lösungsmittels gewannen wir durch Destillation bei 2 Torr nur 6,8 g eines bei 110–120° übergehenden Öls, von dessen weiterer Reinigung wir wegen der beobachteten starken Zersetzungserscheinung absahen.

Es wurden daher 3,5 g des so erhaltenen Säurechlorids in 20 ml absolutem Äther mit einer 0,8N Lösung von Cadmium-dimethyl in Äther versetzt, wobei sich sofort ein weisser amorpher Niederschlag abschied. Nach 3½ Stunden Erhitzen unter Rückfluss hydrolysierten wir mit Eis unter Zusatz von verdünnter Schwefelsäure und extrahierten mit Äther. Aus dem Ätherextrakt konnten nach zweimaliger Kugelrohrdestillation (100–120°/0,2 Torr) 0,5 g eines fast farblosen Öls erhalten werden, das einen Brechungsindex von $n_D^{21} = 1{,}4617$ zeigte, mit Anisaldehyd unter den oben beschriebenen Bedingungen Dianisalaceton lieferte und mit Semicarbazid ein Semicarbazon ergab, das mit dem aus (IVa) erhaltenen identisch war.

5-(3-*Hydroxy*-4-*methyl-phenyl*)-*hepten*-(4)-*on*-(6)-*säure* (VIa). Die *Methylierung der Säure* (VIa) mit einer ätherischen Lösung von Diazomethan lieferte in praktisch quantitativer Ausbeute ein im Kugelrohr bei 170–180°/0,05 Torr übergehendes farbloses Öl, das auf Grund seines Methoxylgehaltes als *Methylester von* (VIa) anzusprechen war. ($C_{15}H_{18}O_4$: Ber. OCH_3, 11,83; Gef. OCH_3, 12,69).

Die *Alkalispaltung von* (VIa) führten wir folgendermassen durch: 1 g der Säure wurde in 20 ml 2N NaOH gelöst und die Lösung 2 Stunden unter Rückfluss erhitzt. Die alkalische Lösung enthielt keine durch Äther extrahierbaren Substanzen. Beim Sättigen mit CO_2 trat eine starke Trübung auf, und der Ätherextrakt dieser bicarbonat-alkalischen Lösung lieferte nach Destillation im Kugelrohr (100–110°/0,2 Torr) 0,2 g eines farblosen Öls. Dieses ergab unter den üblichen Bedingungen mit Semicarbazid-hydrochlorid umgesetzt, weisse Kristalle, die nach Umlösen aus Methanol bei 174–178° schmolzen und mit einem von Langer[10] dargestellten Semicarbazon des (3-*Hydroxy*-4-*methyl-phenyl*)-*acetons* keine Schmelzpunktsdepression zeigten ($C_{11}H_{15}N_3O_2$: Ber. C, 59,71; H, 6,83; N, 18,99. Gef. C, 59,73; H, 6,84; N, 18,92).

Zur *Ozonisierung von* (VIa) wurden 0,25 g der Säure (1 mMol.) in 50 ml trockenem Essigsäureäthylester gelöst und unter Kühlung, zunächst mit Trockeneis-Äthanol, gegen Ende mit Eis, Ozon (0,1% ig) bis zur Sättigung eingeleitet. Die gelbliche Lösung engten wir ohne Erwärmung bei 10 Torr weitgehend ein, versetzten den Rückstand mit einem Gemisch von 8 ml 2N NaOH und 10 ml 10% igem H_2O_2, erwärmten die Lösung 20 Minuten am Wasserbad und extrahierten dann mit Äther. Sowohl dieser Ätherextrakt als auch der nach Sättigung mit CO_2 erhaltene lieferten nur ganz geringfügige Substanzmengen, die nicht weiter untersucht wurden. Aus der mit HCl angesäuerten Lösung erhielten wir durch Ätherextraktion 0,1 g einer gelblichen Substanz, die nach Umkristallisieren aus Äther–Petroläther und mehrmaliger Sublimation weisse Kristalle ergab, die bei 203–209° schmolzen und im Gemisch mit 3-*Hydroxy*-4-*methyl-benzoesäure* keine Misch-Schmp.-Depression ergaben.

Bei weiterer Ätherextraktion der angesäuerten Lösung erhielten wir *Bernsteinsäure*, die ebenfalls durch Schmp. und Misch-Schmp. identifiziert werden konnte.

Die papierelektrophoretische Untersuchung des aus dem Ätherextrakt erhaltenen

Gesamtsäuregemisches ergab viel Bernsteinsäure neben 3-Hydroxy-4-methyl-benzoesäure.

Bei der *katalytischen Hydrierung von* (VIa) nahmen 0,87 g in Methanol mit 10% Pd–Kohle–Katalysator 1,12 Mol. Wasserstoff auf. Nach der üblichen Aufarbeitung destillierte das Hydrierungsprodukt bei 0,02 Torr bei 160° Badtemperatur als farbloses hochviskoses Öl, das nach einigem Stehen in der Kälte erstarrte. Nach mehrmaligem Umlösen aus Äther–Petroläther lag der Schmelzpunkt bei 87–89°. $C_{14}H_{18}O_4$: Ber. C, 67,18; H, 7,25. Gef. C, 67,27; H, 7,38).

5-(3-*Hydroxy*-4-*methyl-phenyl*)-*hepten*-(3)-*on*-(6)-*säure* (Va). Die *Methylierung von* (Va) mit einer ätherischen Lösung von Diazomethan führte zum *Methylester der Säure* (Sdp. 160–170°/0,2 Torr). ($C_{15}H_{18}O_4$; Ber. OCH_3, 11,83. Gef. OCH_3, 11,43)r

Zur *Ozonisierung des Methylesters von* (Va) wurde völlig analog wie bei de. Säure (VIa) verfahren. Auch in diesem Fall konnte aus der alkalischen Lösung nach Behandeln mit H_2O_2–NaOH mit Äther keine Substanz extrahiert werden. Nach Sättigen mit CO_2 wurde durch Ätherextraktion eine ganz geringe Menge eines farblosen Öls erhalten, aus dem sich durch Umsatz mit Semicarbazid ein kristallisiertes Semicarbazon vom Schmp. 170–176° darstellen liess. Die wässrige Lösung der Ozonisierungsprodukte wurde dann angesäuert und abermals mit Äther extrahiert. Der Rückstand des Ätherextraktes bildete eine bräunliche Kristallmasse, aus der durch mehrmaliges Umlösen aus Äther–Petroläther und Sublimation die 3-*Hydroxy*-4-*methylbenzoesäure* isoliert werden konnte. Die papierelektrophoretische Untersuchung des Säuregemisches zeigte die Anwesenheit von *Malonsäure*. In dem Pherogramm waren noch zwei andere, nicht identifizierte Säuren zu finden. Die gebildete Malonsäure konnte auch präparativ durch Überführung in Cinnamalmalonsäure identifiziert werden.

Bei der *katalytischen Hydrierung nahm* (Va) bei Anwesenheit von Pd–Kohle-Katalysator 1 Mol. Wasserstoff auf. Nach der üblichen Aufarbeitung wurde bei der Kugelrohrdestillation (140–160°/0,02 Torr) einr asch kristallisierendes Öl erhalten. Die daraus durch Umlösen aus Methanol–Wasser gebildeten Kristalle schmolzen bei 88–89° und zeigten mit dem Dihydroprodukt von (VIa) keine Misch-Schmp.-Depression.

Zur *Überführung von* (Va) *in* (VIa) wurde 1 g (Va) mit 80 ml 0,2N NaOH 30 Minuten im Stickstoffstrom zum Sieden erhitzt. Nach dem Ansäuern wurde mit Äther extrahiert. Der Rückstand des Ätherextraktes lieferte nach mehrmaligem Umlösen aus Methanol–Wasser eine Säure vom Schmelzpunkt 135–140°, die mit der Säure (VIa) keine Depression des Schmp. ergab.

Lakton der 4-*Hydroxy*-6-*phenyl-hexanon*-(6)-*säure* (IVb). Beim *Kochen einer alkalischen Lösung von* (IVb) unter Rückfluss (½ Stunde) und anschliessender *Wasserdampfdestillation* wurde im Destillat *Acetophenon* erhalten, das nach entsprechender Aufarbeitung durch die Bildungs eines Dinitrophenylhydrazons festgestellt werden konnte.

Die *Oxydation des Laktons* (IVb) wurde in der üblichen Weise in wässrig-alkalischer Lösung mit $KMnO_4$ durchgeführt. Die Ätherextraktion der anschliessend angesäuerten Lösung ergab ein weisses, kristallisiertes Gemisch, in dem durch papierelektrophoretische Untersuchung *Bersteinsäure* und *Benzoesäure* festgestellt werden konnte.

0,3 g des Laktons (IVb) wurden mit 2,5 g $AlCl_3$ in 20 ml abs. Benzol 2 Stunden unter Rückfluss erhitzt. Anschliessend hydrolysierten wir wie üblich mit Eis und HCl

und schüttelten die wässrige Lösung mit Benzol aus. Diese Benzollösung ergab einen Rückstand, der bei der Kugelrohrdestillation (170–175°/0,1 Torr) 0,2 g eines beim Anreiben mit Äther rasch kristallisierenden Destillats lieferte. Dieses *Produkt* (VIII), das bei 140° schmolz, erwies sich als identisch mit dem nach der anschliessenden Vorschrift synthetisierten Produkt.

Zur *Synthese von* (VIII) wurde in ein Gemisch von 4,5 g $AlCl_3$ und 10 ml Benzol eine Lösung von 1,5 g des Chlorids des β-Hydroxy-adipinsäure-laktons in 15 ml Benzol eingetragen. Unter Selbsterwärmung trat eine starke HCl-Entwicklung ein, bis zu deren Beendigung (2 Stunden) am Rückfluss anschliessend erhitzt wurde. Das Gemisch hydrolysierten wir dann mit Eis-HCl und schüttelten die wässrige Lösung mit Benzol aus. Die Kugelrohrdestillation des Rückstandes dieses Benzolextrakts ergab neben einer geringen Menge eines nicht weiter untersuchten Vorlaufs bei 180° 3 Torr 1,1 g eines erstarrenden Destillats, das nach Umlösen aus Aceton–Petroläther weisse, bei 140–141,5° schmelzende Kristalle von (VIIIb) lieferte. ($C_{18}H_{18}O_3$: Ber. C, 76,57; H, 6,43; Äquiv. Gew., 282. Gef. C, 76,24; H, 6,35; Äquiv. Gew., 280).

5-(3-*Hydroxy*-4-*phenyl*-*phenyl*)-6-*phenyl*-*hexen*-(4)-*on*-(6)-*säure*-*äthylester* (*Äthylester der Säure* (VIb)). Beim *Erwärmen des Esters* (0,1 g) in 10 ml 2N NaOH ging die Substanz in Lösung. Das Gemisch wurde dann noch ½ Stunde unter Rückfluss erhitzt und anschliessend ausgeäthert. Die Destillation des Rückstandes des Ätherextrakts (210–230°/0,2 Torr) ergab ein rasch erstarrendes Öl, das nach Umlösen aus Äther–Petroläther bei 149–151° schmelzende Kristalle des *Ketophenols* (VIIb) ergab.

Die *katalytische Hydrierung* des Esters in Alkohol mit Pd–Kohle-Katalysator führte nach 15 Minuten zur Aufnahme von etwa 1 Mol. Wasserstoff und nach weiteren 3 Stunden zur Aufnahme eines zweiten Mols. Wasserstoff. Nach der üblichen Aufarbeitung ergab die Kugelrohrdestillation (230–240°/0,02 Torr) ein glasig erstarrendes farbloses Öl, das nicht zur Kristallisation gebracht werden konnte ($C_{26}H_{28}O_4$: Ber. OC_2H_5, 11,1; Äquiv. Gew., 404 (als Ester). Gef. OC_2H_5, 12,1; Äquiv. Gew., 440).

Beim Ansäuern der mit Natronlauge erwärmten Lösung dieses Öls fiel ein flockiger Niederschlag aus, der in Äther aufgenommen wurde. Nach dem Abdestillieren des Äthers hinterblieb eine schwach gelbe, glasartige Masse. Die Äquivalentgewichtsbestimmung lieferte zwar Werte, die mit der Annahme der Anwesenheit der dem hydrierten Ester entsprechenden Säure übereinstimmten (Ber. 376; Gef. 397), doch war es uns nicht möglich, sie zur Kristallisation zu bringen.

2,4,6-*Trimethyl*-o-*chinol* (IIc)

Das durch die *Einwirkung von Lauge auf das entsprechende Chinolacetat* gebildete *o*-Chinol (IIc) zeigte im IR- wie auch im UV-Bereich Spektren, die analog zu denen des entsprechenden Acetats waren, woraus seine Chinolstruktur gesichert erscheint. In gleicher Weise stimmen auch die Ergebnisse der katalytischen Hydrierung, sowie der Reduktion mit Zink und Schwefelsäure, die an anderer Stelle berichtet wurden,[14] mit der Chinolnatur dieser Verbindung überein. Ihre Acetylierung zum Chinolacetat ist uns aber bisher nicht gelungen. Es kam bei den verschiedenen Versuchen entweder zu überhaupt keiner Umsetzung oder zu weitergehenden Veränderungen.

Bei der *Behandlung des Chinols* (IIc) *mit Lauge bei Siedehitze* unter den beim

[14] A. Siegel und H. Bröll-Keckeis, *Mh. Chem.* **88**, 910 (1957).

entsprechenden Chinolacetat beschriebenen Bedingungen bildete sich in guter Ausbeute die Säure (IIIc), die durch ihr Semicarbazon identifiziert wurde.

2,4-*Dimethyl-hepten*-(3)-*on*-(6)-*säure* (IIIc). Bei der *katalytischen Hydrierung der Säure* (IIIc) in äthanolischer Lösung mit 10%-Pd–Tierkohle-Katalysator nahm diese 1 Mol. Wasserstoff auf. Das Hydrierungsprodukt bildete nach der üblichen Aufarbeitung ein im Kugelrohr bei 130–140°/0,06 Torr übergehendes farbloses Öl. Die Wasserstoffaufnahme muss hierbei an der C=C-Doppelbindung von (IIIc) eingetreten sein, da im Hydrierungsprodukt die Ketogruppe nach wie vor vorhanden war, wie durch die Bildung eines Semicarbazons bewiesen werden konnte.

VOL. 4 1958

Die Analysen wurden von Herrn Univ.-Doz. Dr. G. Kainz im Mikroanalytischer Laboratorium des II. Chemischen Universitätsinstitutes durchgeführt.

Für die Aufnahme der IR-Spektren danken wir Herrn Dr. J. Derkosch, für die Durchführung der papierelektrophoretischen Untersuchungen Herrn Dr. H. Michl.

Tetrahedron, 1958, Vol. 4, pp 66–86. Pergamon Press Ltd., London

VOLATILE CONSTITUENTS OF BLACK-ROTTED SWEET POTATO AND RELATED SUBSTANCES

TAKASHI KUBOTA
Institute of Polytechnics, Osaka City University, Minamiogimachi, Kitaku, Osaka, Japan

(*Received* 4 *February* 1958)

Abstract—From the volatile component of sweet potatoes infected by *Ceratostomella fimbriata* ("black rotted" disease), four β-substituted furans, viz. ipomeamarone (1), batatic acid (45), ipomeanine (47) and β-furan carboxylic acid were isolated. The chemical constitutions of the former three compounds were determined by degradations and by synthesis. The chemical constitution of β-substituted furans, viz. ngaione (52) and myoporon (53), which were isolated from essential oil of *Myoporum* plants were determined and the relation of ipomeamarone, ngaione and myoporone was established.

INFECTION of sweet potatoes, *Ipomoea batatas*, by Ascomycetes, *Ceratostomella fimbriata*, causes the so called "black rot disease" and dark brown spots appear on the potatoes. The affected parts have a specific odour and a very bitter taste. The bitter principle is toxic to animals,[1] acts as an antibiotic towards micro-organisms[2] and has an ascaricidal action.[3] The question of how such a substance is formed inside the potato is of considerable interest in plant physiology[4] and enzyme chemistry.

Hiura[5] was the first to make a chemical study of the bitter principle. He identified it and named it ipomeamarone, and showed it to be an unsaturated ketone. Similar results were reported later by Ohno and Takeuchi[6] and Watanabe and Iwata.[3]

The results of the investigation of the volatile toxic products of black-rotted sweet potatoes are now described, and it has been shown that these volatile components are closely related in chemical structure to the components of the essential oil from *Myoporum* species.

Isolation of volatile components of black-rotted sweet potato

The affected part (120 kg) was cut out, finely sliced and extracted with ether, the extract yielding 1·3 kg of crude oil, which was shaken with sodium hydrogen carbonate solution and separated into crude neutral oil (1·2 kg) and sodium hydrogen carbonate solution containing acidic products. The crude neutral oil was repeatedly fractionated under reduced pressure (10^{-2} to 10^{-3} mm) and afforded fractions having the following data:[7]

Fraction	b.p. (10^{-3} mm)	n_D^{22}	$[\alpha]_D$	Yield (g)
Ipomeanine	69–95°	1·490–1·485	+10°	49
Ipomeamarone	100–103°	1·481–1·478	+22–28°	196

[1] S. Abo and S. Nomura, *J. Verter. Hyg. Ass.* **10**, 17 (1942); S. Nomura and H. Yonemura, *Verter. Sci.* **1**, 5 (1944).
[2] S. Yamashita, *J. Soc. Brewing, Japan* **9**, 88 (1946); I. Yamamoto, S. Suzuki and K. Muramatsu, *Agric. & Hort.* **22**, 515 (1947).
[3] H. Watanabe and H. Iwata, *J. Agric. Chem. Soc. Japan* **23**, 521 (1950).
[4] I. Uritani *et al.*, *J. Agric. Chem. Soc. Japan* **26**, 289 (1953); *Ibid.* **27**, 24, 29, 57, 161, 165, 168, 688, 781, 785, 789 (1954); *Ibid.* **29**, 148, 151, 156, 344, 377, 381 (1955); *J. Biol. Chem. Japan* **41**, 631 (1954); *Ibid.* **43**, 579, 589, 597 (1956).
[5] K. Oze and M. Hiura, *Ann. Rep. Japanese Plant Pathol.* **9**, 123; M. Hiura, *Nogaku*, **7**, 5 (1947); M. Hiura, *Sci. Rep. Gifu Agric. College* No. 50 (1943).
[6] T. Ohno and T. Takeuchi, *Sci. Insect Control* **12**, 26 (1946).
[7] T. Kubota, H. Yamaguchi, K. Naya and T. Matsuura, *J. Chem. Soc. Japan* **73**, 897 (1952).

The ipomeanine portion deposited on standing a small amount of palmitic acid[8]. The sodium hydrogen carbonate solution was extracted with ether to remove the neutral substances completely, acidified with dilute sulphuric acid, and extracted again with ether. The crude acidic oil obtained on evaporation of ether was repeatedly fractionated under a reduced pressure to yield β-furancarboxylic acid (1·0 g) as the sublimate. A fraction of b.p. 90–115° gave crystals of *trans*-cinnamic acid (0·5 g) and the fraction b.p. 115–120° gave crystalline batatic acid (0·8 g).[9] It seemed certain that at least one kind of oily acid with a furan ring is present in this portion, but it has not yet been isolated in a pure state.[10] Valeric and butyric acids in the crude acidic oil were identified by paper chromatography.[9] In this connection, the results of tests for the presence of a furan compound in healthy potatoes were negative.[11]

Structure of ipomeamarone

As stated above, the chief portion is the ipomeamarone fraction, which was repeatedly fractionated, and this fraction was obtained in almost pure state. As shown in Table 1, its physical constants agreed approximately with the data reported by Hiura and Ohno and Takeuchi.

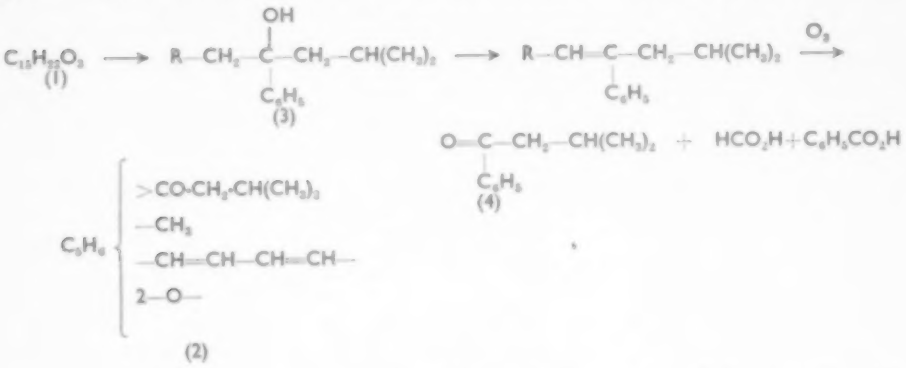
TABLE 1. DATA FOR IPOMEAMARONE FRACTION

Worker	b.p. (°C/mm Hg)	Refractive index	Density	Optical rotation	Semicarbazone m.p. (°C)
Hiura[6]	129°/2·5	—	—	—	131–132
Ohno and Takeuchi[4]	140·4°/6	n_D^{12} 1·4850	d_4^{12} 1·0174	$[\alpha]_D^{12}$ +14·07° (in C_6H_6)	131–132
Writer's	103°/10^{-3}	n_D^{15} 1·4827	d_4^{15} 1·0423	$[\alpha]_D^{25}$ +28·07° (in C_2H_5OH)	133–134

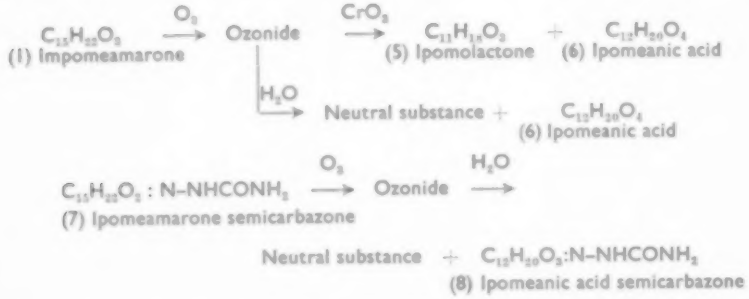
The molecular formula of ipomeamarone (1) agrees with $C_{15}H_{22}O_3$ and it gives a monosemicarbazone of m.p. 133–134°. Since it is negative to Fehling's reagent and fuchsin decolorised with sulphurous acid, it is assumed to possess one ketone group. It does not react with acetic, benzoic or *p*-nitrobenzoic anhydrides, and so the remaining two oxygens must be neutral. Titration of ipomeamarone with bromine in carbon tetrachloride results in the consumption of two molecules of bromine and liberation of two molecules of hydrogen bromide. Titration with perbenzoic acid gives the value of 1·45 and hydrogenation results in the consumption of two molecules of hydrogen. Ipomeamarone forms a maleic anhydride adduct from which the presence of one conjugated double bond may be predicted. Determination of C-methyl group by the Kuhn–Roth method gives a value of 1·85. Oxidation of ipomeamarone with potassium permanganate yields *iso*valeric acid. Based on these observations formula (2) is suggested for ipomeamarone.[12]

[8] T. Kubota and N. Ichikawa, Unpublished work.
[9] T. Kubota and K. Naya, *J. Chem. Soc. Japan*, 77, 86 (1956).
[10] T. Kubota and K. Naya, Unpublished work.
[11] T. Kubota and H. Sakamoto, Unpublished work.
[12] T. Kubota, H. Yamaguchi, K. Naya and T. Matsuura, *J. Chem. Soc. Japan* **74**, 44 (1953).

The action of phenylmagnesium bromide on ipomeamarone (1) and dehydration of the carbinol (3) followed by ozonolysis yields *iso*butyl phenyl ketone (4) and the position of the ketone group is known to be bonded to the *iso*butyl group.[13,14]

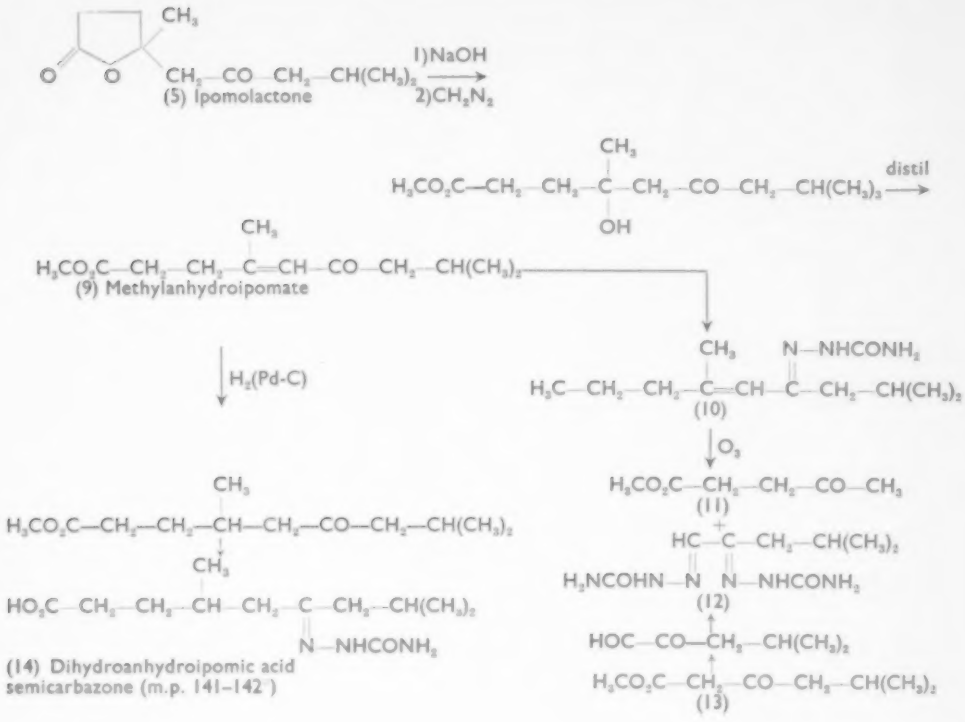


Ozonolysis of ipomeamarone and oxidative decomposition of the ozonide with chromic acid gives ipomolactone (5), $C_{11}H_{18}O_3$, b.p. 108–112°/10^{-3} mm, $n_D^{9.5}$ 1·4610, and ipomeanic acid (6), $C_{12}H_{20}O_4$, b.p. 108–110°/10^{-3} mm, $n_D^{10.0}$ 1·4533. Decomposition of the ozonide with water gives an unknown neutral substance, ipomeanic acid, formic acid and carbon dioxide, but no crystalline derivatives. Ozonolysis of ipomeamarone semicarbazone (7) and decomposition with water gives ipomeanic acid semicarbazone (8) as crystals of m.p. 166–167°, which agreed with the substance obtained by the reaction of ipomeanic acid (6) and semicarbazide hydrochloride.[15]

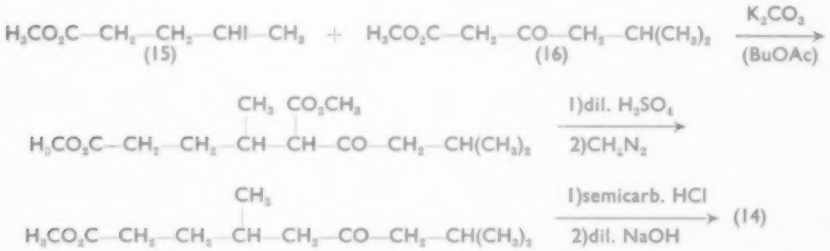


In order to determine the structure of ipomolactone (5), the following experiments were carried out.[16] Ring cleavage of the lactone, esterification and distillation effect dehydration and afford methyl anhydroipomate.[9] Ozonolysis of its semicarbazone (10) gives methyl levulinate (11) and disemicarbazone (12) of *iso*butylglyoxal. (12) was identified with the product synthesised from *iso*valerylacetic acid (13). On the other hand, catalytic reduction of (9) and saponification of the semicarbazone of the product affords dihydroanhydroipomic acid semicarbazone (14), m.p. 141–142°.

[13] T. Ohno and M. Toyao, *Ann. Meet. Agr. Chem. Japan* (1949).
[14] T. Kubota and T. Matsuura, *J. Chem. Soc. Japan* **73**, 530 (1952).
[15] T. Kubota and T. Matsuura, *J. Chem. Soc. Japan* **74**, 101 (1953).
[16] T. Kubota and T. Matsuura, *J. Chem. Soc. Japan* **74**, 105 (1953).

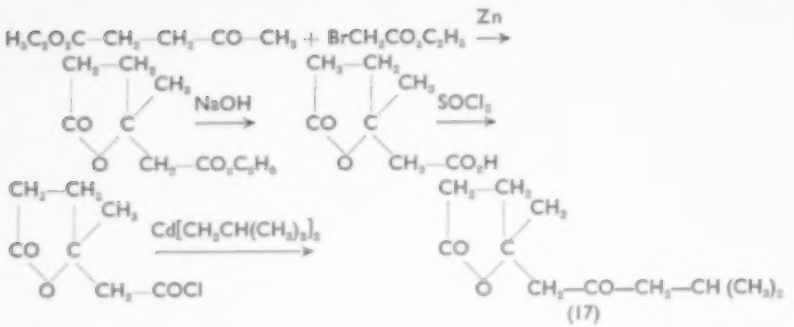


In order to identify the dihydroanhydroipomic acid semicarbazone as (14), it was synthesised from methyl γ-iodovalerate (15) and methyl *iso*valerylacetate (16).[16]



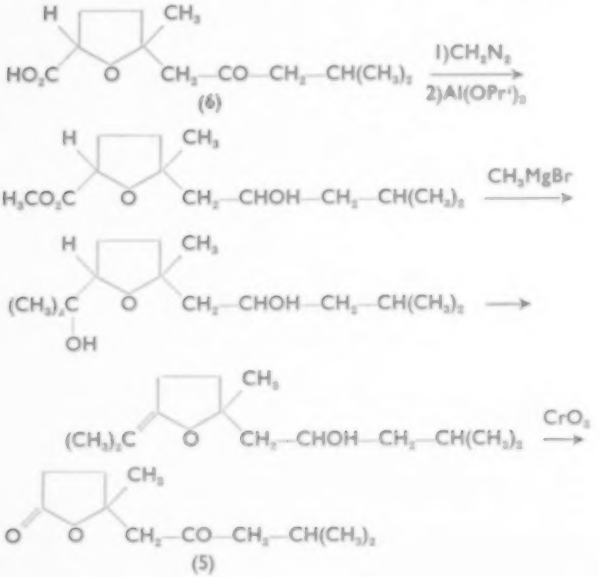
From these results, formula (5) was assumed for ipomolactone and this was confirmed by the synthesis of (±)-ipomolactone.[17] Since ipomolactone does not form any crystalline derivative, the synthetic lactone was converted to dihydroanhydroipomic acid semicarbazone (m.p. 141–142°), which was identified with the same compound from the natural substance.

[17] T. Matsuura, *J. Chem. Soc. Japan* **74**, 668 (1953).



(17)

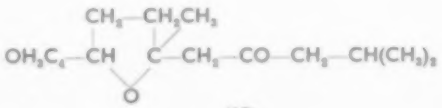
The other fragment obtained on ozonolysis of ipomeamarone, ipomeanic acid (6), $C_{12}H_{20}O_4$, has CH_2O more than ipomolactone (5), $C_{11}H_{18}O_3$. If the structure of ipomolactone is to be represented by (5), ipomeanic acid is assumed to have $=CHCOOH$ in place of $=CO$ in the lactone. This was proved[18] by the fact that one Wieland–Barbier decomposition of ipomeanic acid converts it to the ipomolactone.



(6)

(5)

From the foregoing results, the partial structure of ipomeamarone would be represented by the formula (18) and the doubtful portion is C_4H_3O, which contains a conjugated double bond and one neutral oxygen.

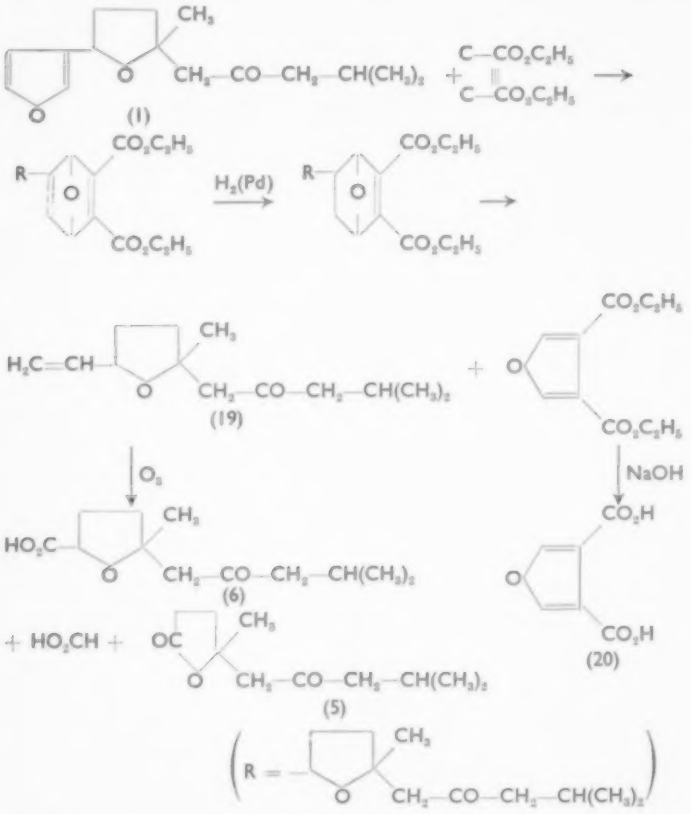


(18)

[18] T. Kubota and T. Matsuura, *J. Chem. Soc. Japan* **74**, 197 (1953).

As previously stated, ipomeamarone is coloured crimson with hydrochloric acid, violet red with *p*-dimethylaminobenzaldehyde[19] and blood red with antimony trichloride,[19] so that this doubtful portion would appear to be a furan ring.

In order to prove this structure and to determine the substituted positions on the furan ring, an Alder–Rickert degradation reaction[20] of ipomeamarone was carried out. This reaction resulted in the formation of furan-3:4-dicarboxylic acid (20), together with a neutral unsaturated ketone (19), indicating this portion to be a β-substituted furan ring. This has established the structure of ipomeamarone to be formula (1).[21]



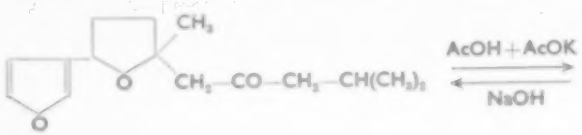
Synthesis of ipomeamarone

When the natural (+)-ipomeamarone (1) is boiled with acetic anhydride and potassium acetate for a long time,[22] the tetrahydrofuran ring is cleaved to form (±)-acetyl*iso*ipomeamarone (21),[23,24] accompanied by racemisation. Saponification

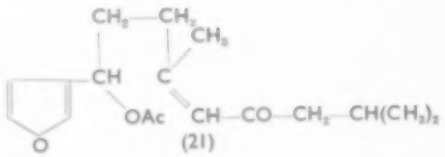
[19] T. Reichstein, *Helv. Chim. Acta* **15,** 1110 (1932); P. Karrer and H. Schmidt, *Ibid.* **29,** 525 (1946).
[20] K. Alder and H. F. Rickert, *Ber. Dtsch. Chem. Ges.* **70,** 1354 (1934).
[21] T. Kubota and T. Matsuura, *J. Chem. Soc. Japan* **74,** 248 (1953).
[22] A. J. Birch, R. Massy-Westropp and S. E. Wright, *Austr. J. Chem.* **6,** 385 (1953).
[23] T. Kubota and T. Matsuura, *J. Chem. Soc. Japan* **78,** 386 (1956).
[24] A. J. Birch, R. Massy-Westropp, S. E. Wright, T. Kubota and T. Matsuura, *Chem. & Ind.* 902 (1954).

of (21) with alkali causes it to revert to (±)-ipomeamarone (22). Since this reaction indicates that there is no change in the steric configuration of αα′-position in the tetrahydrofuran ring, it would seem possible to synthesise ipomeamarone via the compound of type (21).

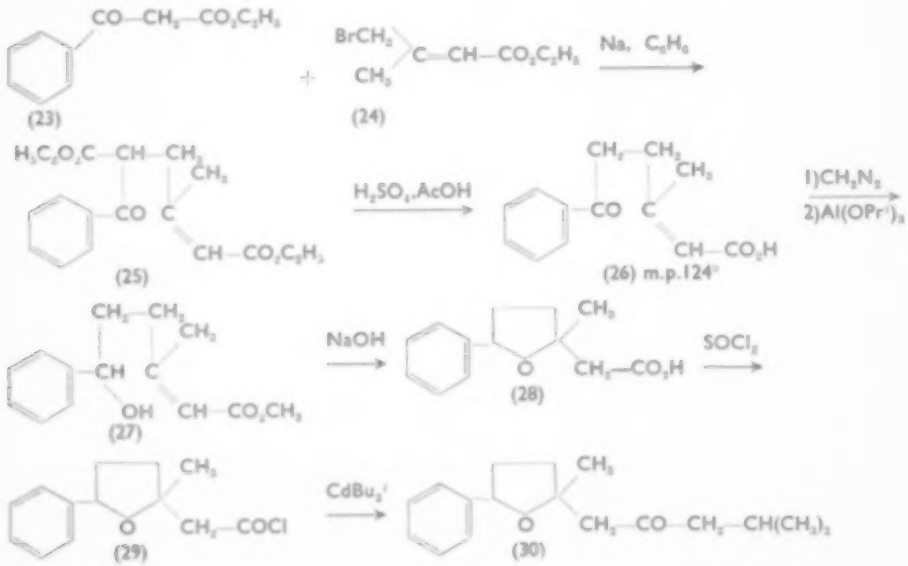
An attempt was first made to synthesise the compound (30) having a benzene ring in place of the furan ring and an oil of b.p. 110°/10^{-3} mm, n_D^{22} 1·5006, was



(1)(+)-Ipomeamarone
(22)(±)-Ipomeamarone



obtained. This substance formed a semicarbazone of m.p. 122–123°, had infra-red absorption maximum at 5·89 μ (5·89 in ipomeamarone) and a strong bitterness, and it was assumed to be the expected substance (30).[25]

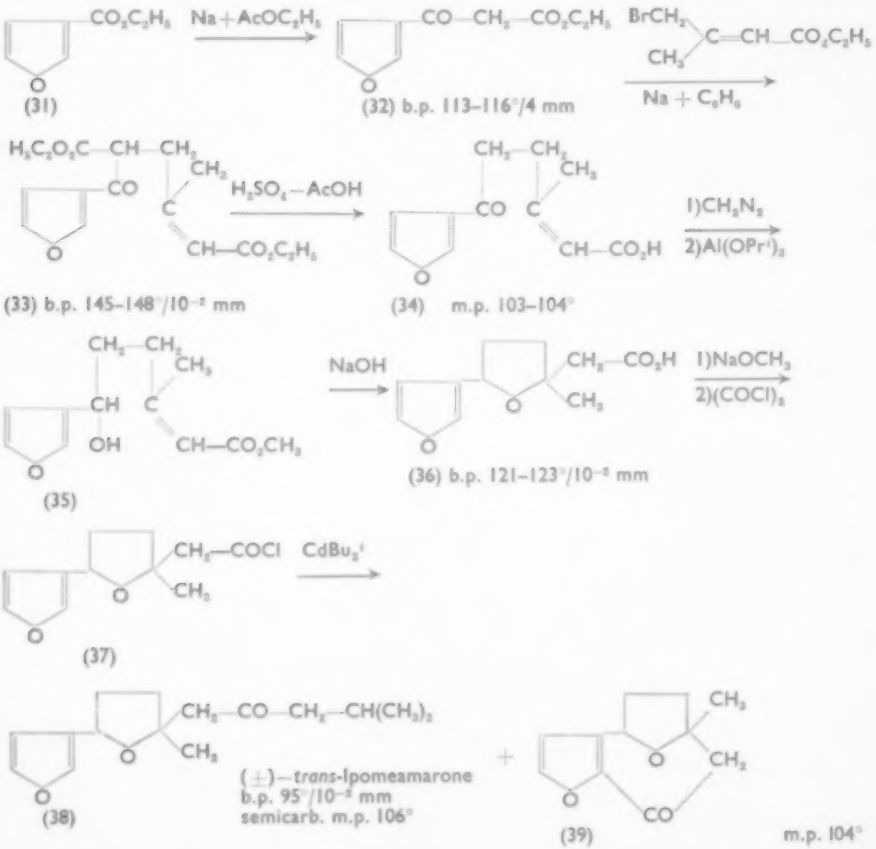


Consequently, this procedure was adopted for the synthesis of ipomeamarone starting with β-furancarboxylic acid (31). Reactions (32) to (36) progressed similarly to the foregoing (23) to (28) to give (36). Attempted chlorination of the carboxylic acid (36) with thionyl chloride resulted in resinification, but chlorination was effected with oxalyl chloride. The reaction of the acid chloride (37) with di*iso*butylcadmium

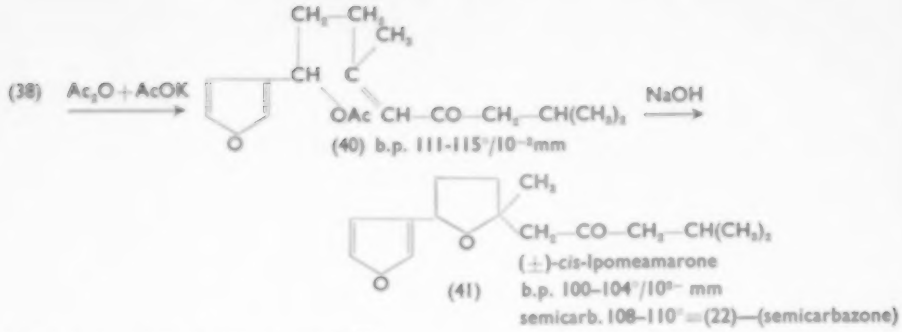
[25] T. Matsuura, *J. Chem. Soc. Japan* **77**, 248 (1955).

gave a yellow liquid (38), b.p. 99–103°/10^{-3} mm, n_D^{11} 1·4910, assumed to be (±)-ipomeamarone, and (39), m.p. 103–104°. (38) possessed a strong bitter taste, its refractive index and colour reactions were the same as those of ipomeamarone, but its infra-red absorption curve, though similar, did not agree with that of ipomeamarone. Its semicarbazone melted at 104–106°, showing depression on admixture with the semicarbazone of natural (±)-ipomeamarone (22), and their infra-red spectra did not agree. It was therefore assumed that (38) is a stereoisomer of ipomeamarone. This stereoisomerism and the structure of (39) will be discussed in the next section. (38) boiled with acetic anhydride and potassium acetate was converted to the acetyl-*iso* compound (40) and its saponification and re-cyclization with alkali gave an oily substance (41). It formed a semicarbazone of m.p. 108–110°, which did not show any depression on mixing with the above-mentioned semicarbazone (m.p. 109·5–110·5°) of (22), and their infra-red absorption curves were completely in agreement.

The foregoing synthesis has definitely established the structure of ipomeamarone to be as represented by the formula (1).[26]

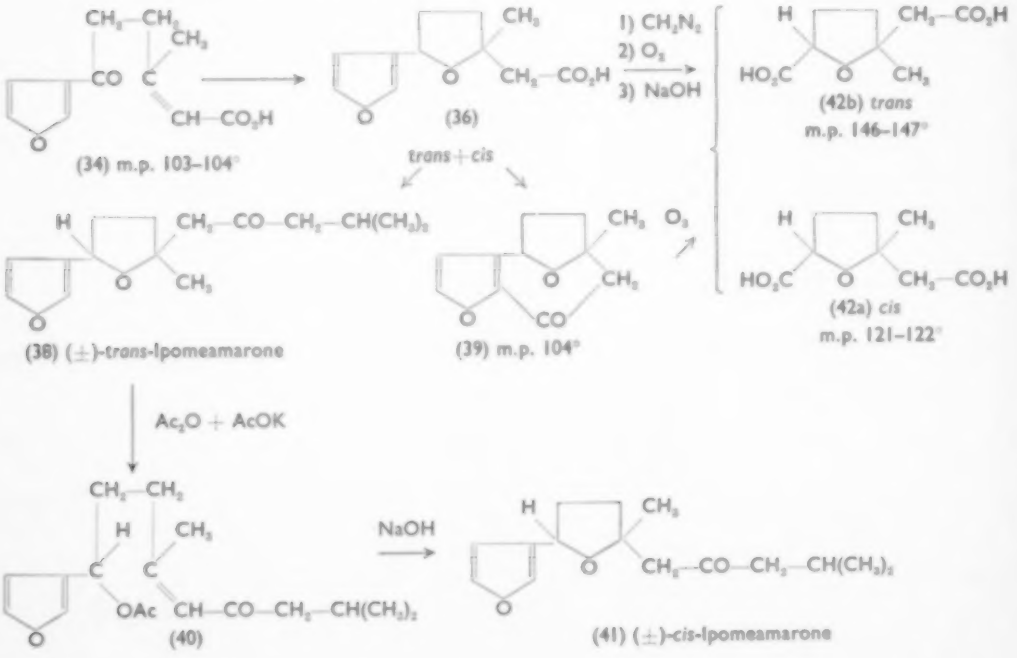


[26] T. Matsuura, *J. Chem. Soc. Japan* **78**, 389 (1956); T. Kubota and T. Matsuura, *Chem. & Ind.* 521 (1956); *J. Chem. Soc.* In press.



Stereoisomerism of ipomeamarone[57]

During the course of the foregoing synthesis of ipomeamarone, application of di*iso*butylcadmium to the acid chloride (37) gave (38), assumed to be the stereoisomer of ipomeamarone, together with (39), m.p. 103–104°. This latter substance is a ketone, giving analytical values corresponding to $C_{11}H_{12}O_3$ (2:4-dinitrophenylhydrazone, m.p. 224°; semicarbazone, m.p. 239°) and is stable to mineral acids; the structural formula (39) is assumed for it. If this formula is correct, it would be sterically impossible for the ring containing the ketone group to be formed unless the furan ring and the carboxymethyl chain are in *cis* configuration. Therefore, the acid chloride (37) must be a mixture of steric isomers in which the side-chains at $\alpha\alpha'$-position of the tetrahydrofuran ring are in *trans* and *cis* configuration. The *trans* isomer would form (38) and the *cis* isomer would give the cyclic ketone (39).



[57] T. Kubota and T. Matsuura, *J. Chem. Soc.* In the press.

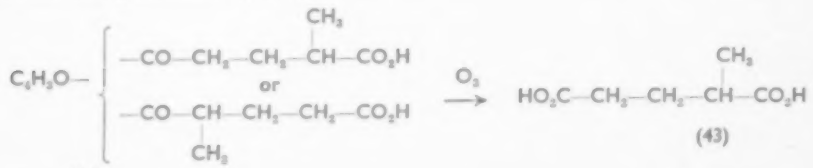
Now to prove whether this assumption is correct or not, the synthetic route for ipomeamarone was reviewed. The unsaturated keto-carboxylic acid (34), m.p. 104°, may be considered as sterically pure, and the carboxylic acid (36) obtained from it by cyclisation does not crystallise, but it is not possible to say whether it is a mixture of stereoisomers or an impure substance. Hence, (36) was submitted to esterification and ozonolysis, the product was saponified, and the acid obtained was fractionally crystallised, from which two crystalline carboxylic acids were obtained, one (42a) melting at 121–122° and the other (42b) at 146–147°. These acids gave the same analytical values ($C_8H_{12}O_5$) and neutralisation values, and were considered to be stereoisomers. Similar ozonolysis of the cyclic ketone (39), in which the furan ring and ketone side-chain are thought to be in *cis* configuration, gave the carboxylic acid (42a) of m.p. 121–122°, from which it is conceivable that (42a) has the *cis* structure and (42b) the *trans* structure.

This experiment has proved that the carboxylic acid (36) is a mixture of *cis* and *trans* isomers, and that the acid chloride (37) is also a mixture. This has also proved indirectly that (±)-*trans*-ipomeamarone (38) was derived from the *trans* acid chloride and the cyclic ketone (39) from the *cis* acid chloride. It may therefore be concluded that the natural (±)-ipomeamarone, obtained by the ring cleavage of (±)-*trans*-ipomeamarone with acetic anhydride and potassium acetate followed by re-cyclisation, is (±)-*cis*-ipomeamarone and the side-chains in natural (+)-ipomeamarone also have *cis* configuration (52).

Structure of batatic acid

Batatic acid is obtained as needle crystals of m.p. 88·5–89·5°, $[\alpha]_D$ 17·5°, in approximate yield of 0·0025 per cent of the sweet potatoes used. Analytical values and molecular-weight determinations suggest the molecular formula of $C_{10}H_{12}O_4$. It forms a mono-2:4-dinitrophenylhydrazone (m.p. 154·5–155·5°), monosemicarbazone (m.p. 177·5–178·5°), and mono-*p*-bromophenacyl ester (m.p. 94–95°). The neutralisation value corresponds to 1 mole of a compound of the above formula. Since its acetylation is impossible, the remaining oxygen must be neutral. Determination by the Kuhn–Roth method suggests the presence of one C-methyl group.

Ozonolysis of batatic acid gave a dicarboxylic acid of formula $C_6H_{10}O_4$, m.p. 81·5–82·5°, $[\alpha]_D$ 19·2°, which was assumed to be (+)-α-methylglutaric acid (43). Its identity was established by the synthesis of (±)-α-methylglutaric acid and by comparison of their infra-red absorption spectra. It follows, therefore, that batatic acid could be represented by (44).



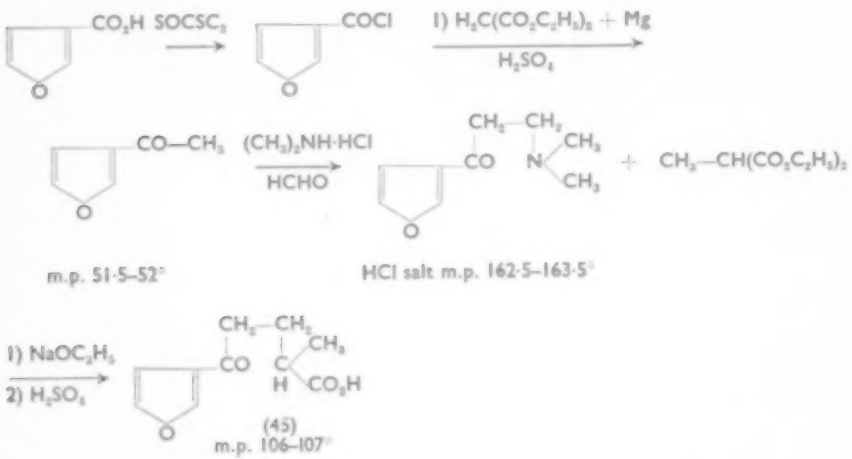
(44) (43)

The portion of formula C_4H_3O is thought to be a furan ring, but batatic acid is negative to the Ehrlich reaction, does not undergo addition with maleic anhydride and has a negative reaction for double bonds. This was assumed to be due to the stabilisation of the furan ring by the presence of a ketone in the α-position of the

side-chain. Its reduction with lithium aluminium hydride converted it into a substance positive to all the above reactions. The correctness of this idea was confirmed with a few furan compounds.[28]

From the foregoing results and the fact that ipomeamarone and ipomeanine are present together in the black-rotted sweet potato, the structural formula (45) seemed to be the most probable[29] and this was proved by synthesis.

The synthesis of (45) was preceded by the synthesis of the corresponding compound possessing a benzene ring in place of a furan ring, i.e., α-methyl-γ-benzoylbutyric acid.[29] Subsequently, (±)-batatic acid (45) was synthesised as shown in the following scheme:



The infra-red absorption curve of synthetic (±)-batatic acid agreed completely with that of (+)-batatic acid, thus establishing the structure of (+)-batatic acid.[30]

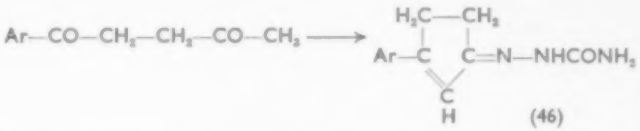
Structure of ipomeanine[31]

Purification of the low-boiling fraction of the neutral portion from the ether extract of black-rotted sweet potato gave an oil of b.p. 74–79°/10^{-3} mm, n_D^{15} 1·4975, $[\alpha]_D$ + 3·86°. When the oil is inoculated with crystalline ipomeanine (synthetic), it crystallises with loss of optical activity. The decomposition experiment described below was carried out with an oily substance with $[\alpha]_D$ + 3–6°.

Ipomeanine gives analytical values corresponding to $C_9H_{10}O_3$ and forms a bis-2:4-dinitrophenylhydrazone, $C_{21}H_{18}O_9N_8$, m.p. 232–234°. Its reaction with semicarbazide is abnormal and the product is a dehydrated monosemicarbazone, $C_{10}H_{11}O_2N_3$, m.p. 215–216°. This could be explained by assuming that it is a reaction similar to that observed by Borsche *et al.*,[32] with 1:4-diketones. The semicarbazone would be represented by (46). Ipomeanine gives the iodoform reaction, suggesting

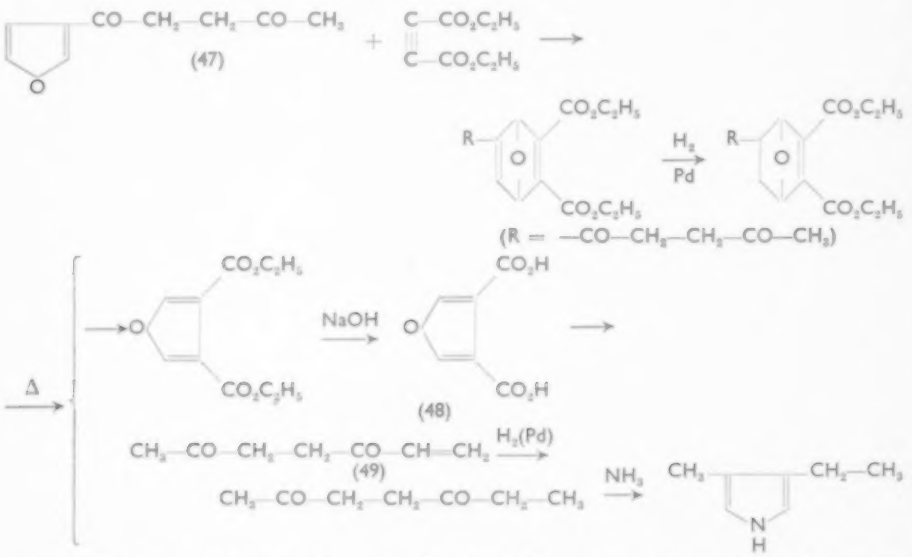
[28] T. Kubota and K. Naya, *Chem. & Ind.* 1427 (1954); *J. Chem. Soc. Japan* **77**, 86 (1955).
[29] K. Naya and T. Kubota, *J. Chem. Soc. Japan* **77**, 252 (1955).
[30] K. Naya, *J. Chem. Soc. Japan* **77**, 759 (1955).
[31] T. Kubota and N. Ichikawa, *Chem. & Ind.* 902 (1954); *J. Chem. Soc. Japan* **75**, 447 (1954)
[32] W. Borsche and W. Menz, *Ber. Dtsch. Chem. Ges.* **41**, 199 (1908).

the presence of a CH_3CO-type ketone. The remaining oxygen is assumed to be neutral from various colour reactions. Ipomeanine absorbed 2 moles of hydrogen by catalytic reduction to form tetrahydroipomeanine (semicarbazone, m.p. 174–175°) and reacted with maleic anhydride to give an addition product of m.p. 117–118°. Oxidation of ipomeanine with potassium permanganate gave levulic acid and ozonolysis gave levulic acid and formic acid. From the result of these oxidative decompositions, the colour reaction, the abnormality of its semicarbazone and the

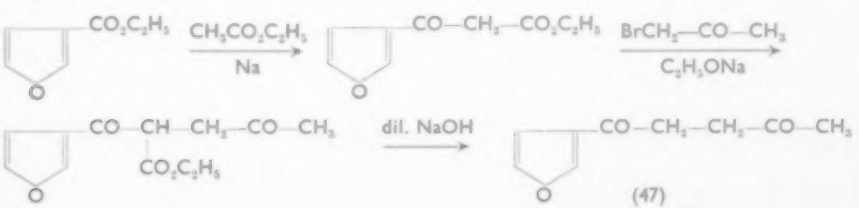


(46)

fact that this is a sub-component of ipomeamarone, the structure of ipomeanine could be assumed to be (47). In order to prove this, ipomeanine was submitted to an Alder–Rickert degradation. The reaction proceeded as expected, and furan-3:4-dicarboxylic acid (48) and a neutral unsaturated ketone (49) were obtained. Since the latter ketone gave a positive pine-splinter test after reduction of its double bonds and application of ammonia by forming a saturated ketone it seems almost certain that the structural formula (47) is correct.



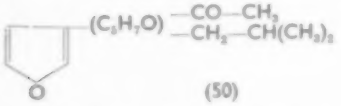
In order to prove this structure, synthesis of (47) was carried out by the following route.[31]:



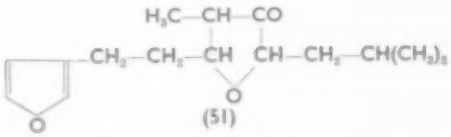
The synthesised product melted at 41–42°, and gave no depression of the melting point on admixture with the natural product; their infra-red absorption curves were in complete agreement.

Structure of ngaione

In 1925, McDowall[33] obtained a ketone, $C_{15}H_{22}O_3$, which he named ngaione, from the components of the essential oil from the leaves of a New Zealand shrub, *Myoporum laetum* Forst (called ngaio by the natives), and Brandt and Ross[34] gave it a partial structure (50) for it in 1949. Later, in 1953, Birch *et al.*[35] isolated ngaione from *Myoporum acuminatum* R. Br. and *Eremophila latrobei* (both found in Australia) and put forward the structure (51) for it.



(50)



(51)

As was also pointed out by Ohno,[36] physical constants of ipomeamarone and ngaione are similar, with the exception of optical rotations, as seen from the following data:

	b.p. (°C/mm)	n_D	d_4^{25}	$[\alpha]_D$	Semicarbazone m.p. (°C)	$[\alpha]_D$
Ngaione	159–160/10	1·4769(25°)	1·0231	−25·1°(C_2H_5OH)		
				−12·3°(C_6H_6)	132·5–133	−66·2°
Ipomeamarone	145–149/5	1·4807(20°)	1·0290	+28·06°(C_2H_5OH)		
				+11·07°(C_6H_6)	133–134	+85°

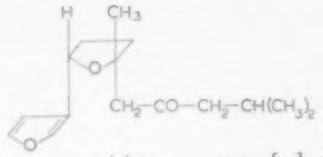
The reactivity of these two substances was compared in co-operation with Birch and his co-workers and it was concluded that the two substances might be diastereoisomers.[37]

The chief basis for this assumption is the fact that the semicarbazone (8), $C_{13}H_{23}O_4N_8$ (the two active centres remain intact), of ipomeanic acid obtained by ozonolysis of the two ketones give different data, one from ipomeamarone melts at 167°, $[\alpha]_D$ −81° (in ethanol) and that from ngaione melting at 171–172°, $[\alpha]_D$ −40° (in ethanol).

It was later found that the infra-red absorption curves of the semicarbazones of ipomeamarone and ngaione were identical and it was concluded that these two substances are optical isomers. Considering the foregoing results on the synthesis of ipomeamarone, both ipomeamarone and ngaione should belong to the *cis*-system (52).[38] It is still not clear what causes the difference in the optical rotation of the semicarbazone of ipomeanic acid, but it may be possible that the semicarbazone

[33] F. McDowall, *J. Chem. Soc.* 200 (1925); *Ibid.* 731 (1927); *Ibid.* 1324 (1928).
[34] C. W. Brandt and D. J. Ross, *J. Chem. Soc.* 2778 (1949).
[35] A. J. Birch, R. Massy-Westropp and S. E. Wright, *Austr. J. Chem.* **6**, 385 (1953).
[36] T. Ohno, *Bull. Chem. Soc. Japan* **25**, 222 (1952).
[37] A. J. Birch, R. Massy-Westropp, S. W. Wright, T. Kubota and T. Matsuura, *Chem. & Ind.* 902 (1954).
[38] T. Kubota and T. Matsuura, *Chem. & Ind.* 521 (1956); *J. Chem. Soc.* In the press.

from ngaione is partially racemised, since the α-carboxylic acid of tetrahydrofuran is comparatively easily racemised.

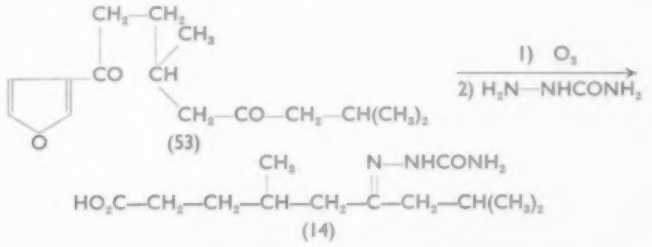


(52) (+) Ipomeamarone: $[\alpha]_D$ + 28°
(-) Ngaione: $[\alpha]$ -25°

Component of Myoporum bontioides *and structure of myoporone*[39]

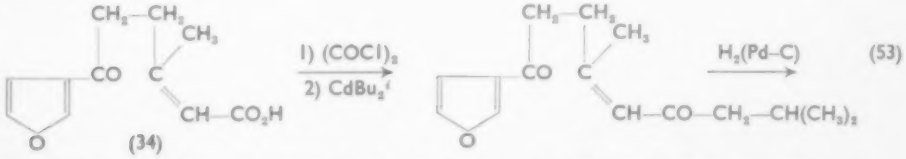
As was mentioned in the preceding section, studies have been made on the components of the essential oil of *Myoporum* spp. and ngaione and β-furancarboxylic acid[35] have been isolated. As a sample of ngaione was desired and some interest was felt for the components of the essential oil from the leaves of *Myoporum bontioides* A. Gray, the only Myoporum plant in Japan, an examination of this oil was made. Unexpectedly, however, only a minute amount of ngaione was found in the essential oil and the chief component was found to be an unknown ketone, $C_{15}H_{22}O_3$ (b.p. 117–119°/10^{-2} mm, n_D^{21} 1·4770, $[\alpha]_D$ 0°), which was named myoporone, and its structure was examined. Myoporone (53) forms two 2:4-dinitrophenylhydrazones, thought to be dimorphs:[40] a red α-compound of m.p. 193° and an orange-yellow β-compound of m.p. 193°, which turns reddish at 143–145°. Myoporone shows no optical rotation at the D-line, but its 2:4-dinitrophenylhydrazone (α-form) has $[\alpha]_D^{23}$ −28·2°. It gives a positive Ehrlich reaction and was assumed to have a structure closely related to that of ngaione.

Ozonolysis of myoporone afforded one keto acid whose semicarbazone, m.p. 139–141°, agreed with the semicarbazone (14), m.p. 141–142°, of dihydroanhydroipomic acid derived from ipomolactone. It may therefore be assumed that the structure of myoporone would be represented by (53).



(53) (14)

In order to prove this assumption, the synthesis of myoporone was undertaken[39] from the keto-carboxylic acid (34), intermediate in the synthesis of (±)-ipomeamarone.



(34) (53)

[39] T. Kubota and T. Matsuura, *Chem. & Ind.* 491 (1957); *Bull. Chem. Soc. Japan* **31**, 491 (1958).
[40] W. Dirscherl and H. Nahm, *Ber. Dtsch. Chem. Ges.* **73**, 448 (1940).

TABLE 2. INFRA-RED ABSORPTION SPECTRA OF SUBSTITUTED FURANS

Substituents		Wavelength (μ)				
α	β					
—	—	3·16	6·33	6·91	11·47	13·79
$-CH_2OH$	—	—	—	6·64	11·31	13·4–13·6
$-CH_2OCOCH_3$	—	3·19	6·41	6·65	11·30	13·3–13·5
—CHO	—	3·16	6·40	6·82	11·32	13·10
—COOH	—	3·16	6·34	6·79	11·26	13·10
$-COOC_2H_5$	—	3·19	6·39	6·79	11·32 (11·52)	13·42
$-COCH_2CO_2C_2H_5$	—	3·18	6·37	—	11·30	13·00
$-COCHCH_2CO_2CH_3$ ($CO_2C_2H_5$)	—	3·18	6·38	—	11·30	13·00
—	—COOH	—	6·40	6·64	11·42	13·00 (13·35)
$-CH_3$	—COOH	—	6·20	6·58	11·17	13·10 (13·50)
—	$-CO_2C_2H_5$	3·18	6·42	6·65	11·44	13·13
$-CH_3$	$-CO_2C_2H_5$	3·19	6·23	6·57	11·13	13·55
—	$-COCH_3$	3·21	6·41	6·63	11·44	13·13
—	—COOH —COOH	3·18	6·41	6·62	11·30	13·15
—	$-CO_2C_2H_5$ $-CO_2C_2H_5$	3·18	6·49	—	11·20	13·12
$-CO_2C_2H_5$ $-COCH_3$	—	?	?	?	?	13·10
$-COCH_2$	$-CO_2C_2H_5$	3·18	6·51	—	11·44	13·02
$-COCH_2$	$-CO_2C_2H_5$ $-CO_2C_2H_5$	3·18	6·51	—	11·24	13·00
$-CHOHCH_2$	$-CO_2C_2H_5$ $-CO_2C_2H_5$	—	—	—	11·23	13·12
—COOH —COOH	—COOH	—	—	—	11·24	?
—COOH —COOH	—COOH —COOH	—	—	—	11·52	13·20

TABLE 3. INFRA-RED SPECTRA OF FURAN DERIVATIVES

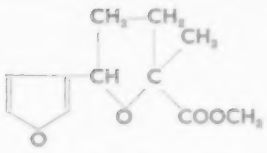
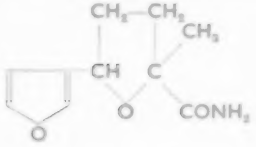
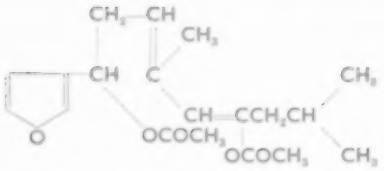
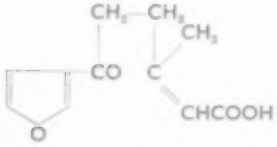
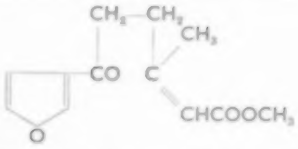
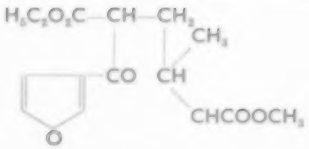
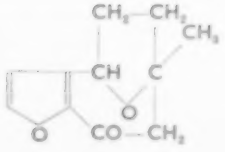
Compounds	Wavelength (μ)				
	3·19	—	6·62	11·42	12·60(?)
	3·19	6·41	6·65	11·37	12·60(?)
	3·19	6·40	6·63	11·42	13·62
	3·18	6·40	6·62	11·44	13·26
	3·18	6·40	6·62	11·44	13·42
	3·18	6·41	6·64	11·44	13·40
	3·21	—	6·67	11·32	13·13

TABLE 3 (continued)

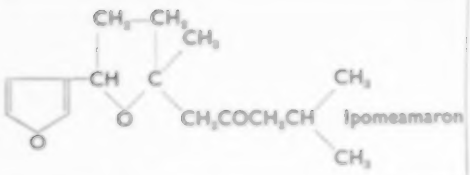
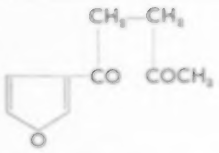
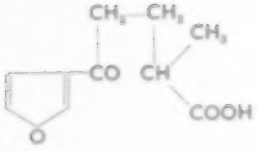
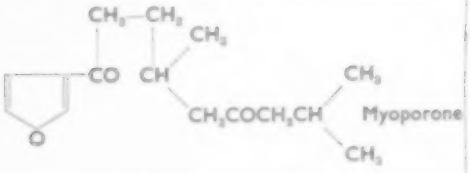
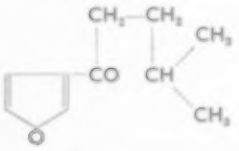
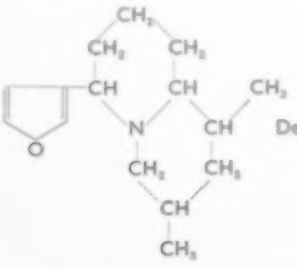
Compounds	Wavelength (μ)				
 Ipomeamaron	3·19	6·40	6·63	11·42	13·62
 Ipomeanine	3·19	6·40	6·62	11·44	13·30
 Batatic acid	3·20	6·40	6·62	11·46	13·20
 Myoporone	3·19	6·41	6·64	11·45	13·00
 Perilla ketone	3·18	6·40	6·63	11·45	12·90
 Desoxynupharidine	3·19	6·37	6·67	11·42	12·70, 13·08, 13·80
Columbin, $C_{20}H_{22}O_6$	3·19	—	6·65	11·42	12·73, 13·30

TABLE 3 (continued)

Compounds	Wavelength (μ)				
Limonin, $C_{26}H_{30}O_8$	—	—	6·66	11·44	13·16
Limonilic acid, $C_{26}H_{28}O_9$	3·18(?)	—	6·66	11·48	12·95
Methyl limonilate, $C_{27}H_{32}O_9$	3·20	—	6·66	11·46	12·97
Dehydrolimonin, $C_{26}H_{28}O_8$	3·13	—	6·66	11·45	13·13, 13·32
Limonin–$LiAlH_4$, $C_{26}H_{40}O_8$	3·12(?)	—	6·67	11·40	12·92
Limonin–$LiAlH_4$ acetate, $C_{34}H_{50}O_{12}$	3·18	—	6·67	11·40	12·93
Obacunone, $C_{26}H_{30}O_7$	3·18	—	6·66	11·42	13·12
Obacunone–$LiAlH_4$, $C_{26}H_{40}O_7$	?	—	6·72(?)	11·45	12·95

The bis(2:4-dinitrophenylhydrazone) of the synthetic product consists of red crystals, m.p. 208–210° (thought to be the α-compound), and the infra-red absorption spectra of the natural and the synthetic product were in complete agreement. It was thereby established that the structure of myoporone is represented by (53).

Infra-red absorption spectra of furan derivatives[41]

The following three bands have been selected as the characteristic absorption bands of the furan ring in this laboratory: (*a*) around 3·20 μ (C–H), (*b*) around 6·40 and 6·62 μ (aromatic ring) and (*c*) 11·3–11·5 μ (?).

The values around these absorption bands by various furan compounds investigated in this laboratory are indicated in Tables 2 and 3.

CONCLUSIONS

The foregoing experimental results have clarified the chemical composition of the components of black-rotted sweet potato and the components of the essential oil of *Myoporum bontioides* A. Gray, which are closely related. The chief substances that have been confirmed are (1), (45), (47), (52), (53) and β-furancarboxylic acid. Ipomeamarone, ngaione and myoporone are all normal sesquiterpenes in which the isoprene units are bonded in head-to-tail linkage, and the fact that the chain-end in these substances has cyclised to a furan ring is a specific characteristic. These are the first group of substances of this type of terpene to be found in nature (1951).

Ipomeamarone was formed as a result of abnormal metabolism in a sweet potato caused by the parasitic growth of *Ceratostomella fimbriata* and produced through consumption of its own starch.

Healthy sweet potatoes do not contain any furan compounds or terpenes,[11] no doubt through operation of the Krebs cycle, which has been shown by Uritani

[41] M. Yamaguchi, *Japan Analyst*, 7, 211 (1958).

and others[8] to take place when the cell functions in the sweet potato become abnormal through the effect of the fungus, the Krebs cycle being inhibited with the resultant formation of terpenes. Bonner, Lynen, Birch and others have studied the formation mechanism of terpenes from acetic acid through acetoacetic acid and mebalonic acid, and the results of these investigations may be applied to the formation of ipomeamarone during abnormal metabolism in the sweet potato.

On the contrary, ngaione and myoporone are considered to be the normal metabolic accumulation of a higher vegetable, *Myoporum*. The interesting point is that while the *dextro*rotatory (+)-ipomeamarone is accumulated in the black-rotted sweet potato, a *laevo*rotatory (−)-ngaione (= (−)-ipomeamarone) is accumulated by *Myoporum*. This may offer a key to elucidate the problem of biological reactions in the future.

Batatic acid, ipomeanine and β-furancarboxylic acid are considered to have been formed by the secondary oxidation of ipomeamarone in black-rotted sweet potatoes (or in *Myoporum* in the case of β-furancarboxylic acid), since their content is rather small. This cleavage of the side-chain is also an interesting problem and this mechhanism is a problem to be solved in the future.

Acknowledgements—I express my deep gratitude to Professor A. J. Birch, Manchester University, for supplying the sample of the semicarbazones of ngaione and for valuable discussions. I am also indebted to Miss Dorothy Mizoguchi for preparing the English manuscript.

Tetrahedron, 1958, Vol. 4, pp. 87–104. Pergamon Press Ltd., London

ANNOTININE—II

THE COMPLETE STRUCTURE

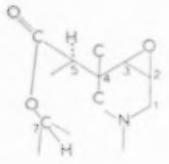
K. WIESNER, Z. VALENTA, W. A. AYER,* L. R. FOWLER† and J. E. FRANCIS†
Organic Chemistry Laboratory, University of New Brunswick, Canada

(*Received* 5 *February* 1958)

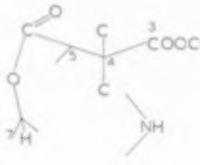
Abstract—The structure (LII) is shown unambiguously to be the correct representation of annotinine.

IN the first full account[1] of our studies on annotinine we showed conclusively that this compound is represented by the partial structure (I). In this partial structure the lactone carboxyl is in the less stable configuration, and annotinine derivatives, in which this is possible, readily epimerise at carbon 5.

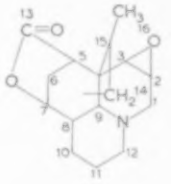
It has been further demonstrated that C_4 is probably a quaternary carbon, since the amino ester (II) proved resistant to saponification.



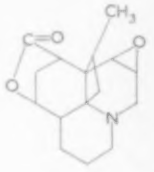
I



II



III



IV

In a preliminary communication[2] we extended the partial formula (I) to (III).

In the partial structure (III) only one carbon–carbon bond between C_{14} and C_9, C_8 or C_6 remained to be closed.

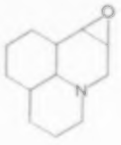
Early in 1957 we presented evidence in another preliminary communication,[3] which rigorously corroborated the partial structure (III) and permitted us unambiguously to extend it to (IV). Finally, in a paper submitted after the appearance in print of our complete structure (IV),[3] Przybylska and Marion[4] corroborated this formula by X-ray crystallography.

In the present communication we wish to give a detailed account of the experiments that permit the derivation of the complete structure (IV) for annotinine. An interpretation of these data makes possible also the assignment of configuration to most of the asymmetric centres.

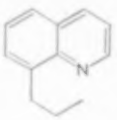
* Holder of an Eli-Lilly Postdoctoral Fellowship.
† Holder of a National Research Council Studentship.

[1] Z. Valenta, F. W. Stonner, C. Bankiewicz and K. Wiesner, *J. Amer. Chem. Soc.* **78**, 2867 (1956).
[2] K. Wiesner, Z. Valenta, W. A. Ayer and C. Bankiewicz, *Chem. & Ind.* 1019 (1956).
[3] K. Wiesner, W. A. Ayer, L. R. Fowler and Z. Valenta, *Chem. & Ind.* 564 (1957).
[4] M. Przybylska and L. Marion, *Canad. J. Chem.* **35**, 1075 (1957).

The first indication that annotinine contains the perhydrojulolidine system (V) came from dehydrogenation reactions.



V

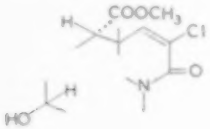


VI

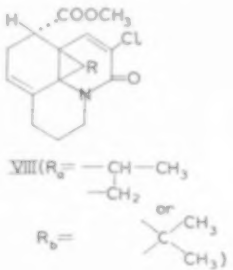
At the very beginning of our work we showed that 8-*n*-propylquinoline (VI) is formed in good yield besides other products in a selenium dehydrogenation of annotinine.[5]

Compound (VI) may be obviously derived from annotinine in two different ways, if the alkaloid contains the partial structure (V).

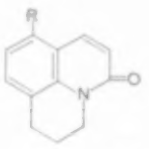
We have obtained an even more striking confirmation of the presence of system (V) in annotinine in the following manner. The hydroxy ester, $C_{17}H_{22}NO_4Cl$, which we have described previously[1] and which is represented by the partial structure (VII), was subjected to dehydration with phosphorus pentoxide in boiling xylene.



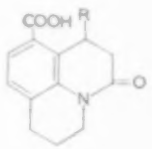
VII



VIII (R_a = —CH(CH$_3$)—CH$_2$— or R_b = —C(CH$_3$)$_2$—)



IX (R = —COOH)
X (R = H)



XI (R = H)
XII (R = CH$_3$)

The product of this reaction was a crystalline anhydro ester (VIII), $C_{17}H_{20}NO_3Cl$, obtained in a yield of 60 per cent. Compound (VIII) had practically the same ultra-violet absorption spectrum [λ_{max} 227 mμ (log ε 4), shoulder 280 mμ (log ε 2·9)] as compound (VII) and showed also very similar peaks in the carbonyl region of the infra-red [1735 cm^{-1} (ester), 1658, 1620 cm^{-1} (conjugated lactam)]. It has been possible to show rigorously (*vide infra*) that (VIII) was formed merely by elimination of water and that it has the same skeletal structure as annotinine.

Palladium dehydrogenation of the anhydro-ester (VIII) gave a good yield of the quinolone acid (IX). The structure of (IX) follows from the decarboxylation of this compound to the known trimethylenequinolone (X), which was identified by comparison with an authentic specimen.[6] It is reasonable to assume that the carboxy group in (IX) is located at C_5, since this position corresponds to the rigorously established partial formula of the compounds (VII) and (VIII). This assumption is supported by the spectroscopic properties of the dihydroquinolone acid (XI), which may be prepared from (IX) by a reduction with sodium amalgam. Compound (XI) has an ultra-violet spectrum [λ_{max} 236 mμ (log ε 4·2), shoulder 258 mμ (log ε 4·1),

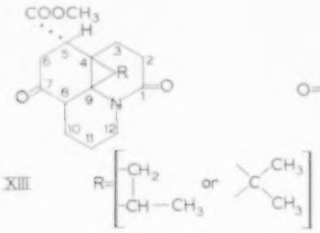
[5] C. Bankiewicz, D. R. Henderson, F. W. Stonner, Z. Valenta and K. Wiesner, *Chem. & Ind.* 544 (1954).
[6] L. G. S. Brooker and D. W. Hezeltine, *Chem. Abstr.* **48**, 1184 (1954).

λ_{max} 300 mμ (log ε 3·3)] identical and an infra-red spectrum very similar to the compound (XII), which we have previously synthesised.[7]

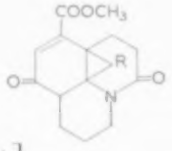
If we assume that no rearrangement has taken place in the palladium dehydrogenation, three out of the four rings of annotinine are defined in the quinolone acid (IX). The fourth ring must now be added by attaching a bridge at two points to the skeleton of compound (IX). Since annotinine is known to have one C-methyl group, this bridge may have either the structure Ra or Rb [in formula (VIII)].

One point at which the bridge must be attached is C_4, since, as we already stated, this carbon has been shown to be quaternary.

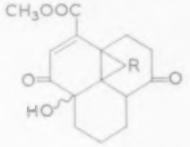
The experiments to be described in the sequel show rigorously that the second point of attachment is at C_9. They also provide us with a rigorous confirmation of the skeletal structure suggested by the results of the dehydrogenation reactions just described. Thus we may formulate the anhydro ester by the structural formula (VIII). The position of the double bond in (VIII) follows from oxidation studies (*vide infra*).



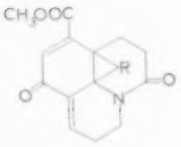
XIII



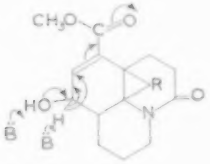
XIV



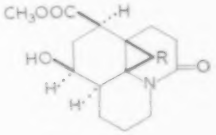
XV (–OH, R *cis*)
XVI (–OH, R *trans*)



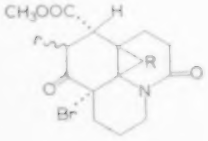
XVII



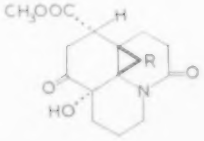
XVIII



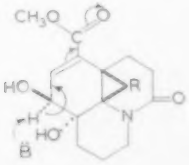
XIX



XX (r = Br)
XXI (r = H)

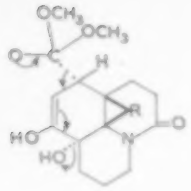


XXII

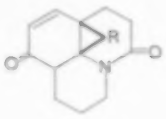


XXIII

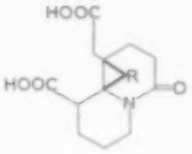
[7] Z. Valenta, K. Wiesner, C. Bankiewicz, D. R. Henderson and J. S. Little, *Chem. & Ind.* (*B.I.F. Review No.*) R40 (1956).



XXIV



XXV



XXVII

The key compound in the series of experiments to be discussed is the keto ester $C_{17}H_{23}O_4N$ (m.p. 200°), which we have described previously[1] and which may now be formulated as (XIII). It will be noted that the carbomethoxy group of (XIII) has a configuration epimeric to the natural configuration of the lactonic group in annotinine.

The oxidation of (XIII) with selenium dioxide in dioxan gave a mixture of four products, which were separated by chromatography on alumina. The first of these compounds was a keto ester, $C_{17}H_{21}O_4N$, m.p. 144–145° [ultra-violet spectrum, λ_{max} 242 mμ (log ε 3·9); infra-red spectrum, 1725 cm^{-1} (ester), 1698 cm^{-1} (ketone), 1640 cm^{-1} (lactam)], to which we assigned the structure (XIV).

While the ultra-violet and infra-red data were in good agreement with a conjugated keto ester such as is portrayed in (XIV), it was nevertheless not possible to exclude on the basis of spectra alone an $\alpha\beta$-unsaturated ketone with an unconjugated ester group. The following chemical transformations prove rigorously the presence of the conjugated keto ester chromophore. Compound (XIV) was reduced with sodium borohydride to the corresponding allylic alcohol (XVIII), m.p. 235–236° [ultra-violet spectrum, λ_{max} 222 mμ (log ε 4·0); infra-red spectrum 1718 cm^{-1} (ester), 1624 cm^{-1} (lactam)]. Treatment of (XVIII) with sodium methoxide in methanol under reflux gave the original keto ester (XIII). Now it is not conceivable that an unconjugated allylic alcohol could be isomerised by base to the corresponding ketone. On the other hand, in the case of a conjugated allylic alcohol ester such as (XVIII), one can easily envisage two mechanisms by which such a transformation may be accomplished. They are indicated by arrows in the formula (XVIII) and are self-explanatory.

The second product of the selenium dioxide treatment of compound (XIII) was a keto ester, $C_{17}H_{19}O_4N$, m.p. 127–128° [ultra-violet spectrum, λ_{max} 251 mμ (log ε 4·0); infra-red spectrum, 1731 cm^{-1} (ester), 1672 cm^{-1} (ketone), 1625 cm^{-1} (lactam)]. On the basis of the ultra-violet and infra-red spectra, the structure (XVII) was assigned to this compound. A striking confirmation of this structure, which at the same time clarified the configuration of three asymmetric centres of annotinine, was achieved as follows. Compound (XVII) was vigorously hydrogenated over platinum oxide in glacial acetic acid. In this hydrogenation it is reasonable to assume that the hydrogen has been added from one side of the molecule and opposite to the C_4–C_9 bridge. Thus the relative configuration of C_5, C_7 and C_8 in the hydrogenation product must be as indicated in the structure (XIX). Now the hydrogenation product (XIX) is identical with a hydroxy ester $C_{17}H_{25}O_4N$, m.p. 166°, which we described previously and which has been shown[1] to possess the carbomethoxy group (and of course all other asymmetric centres) in the natural configuration of annotinine. Consequently, the lactone ring in annotinine must be *cis* to the C_4–C_9 bridge and *trans* to the hydrogen at C_8.

The last two products of the selenium dioxide reaction were two isomeric hydroxy-keto esters $C_{17}H_{21}O_5N$. These compounds are represented by the structures (XV) and (XVI) and they are regarded as C_8 epimers. The properties of the two compounds are as follows:

(XV), m.p. 212–213°; ultra-violet spectrum, λ_{max} 244 mμ (log ε 3·9); infra-red spectrum, 1726 cm^{-1} (ester), 1709 cm^{-1} (ketone), 1640 cm^{-1} (lactam).

(XVI), m.p. 246·5–247°C; ultra-violet spectrum, λ_{max} 242 mμ (log ε 3·8); infra-red spectrum, 1732 cm^{-1} (ester), 1701 cm^{-1} (ketone), 1628 cm^{-1} (lactam).

A much more convenient method of preparation of compound (XV) is the alkaline hydrolysis of the dibromide (XX), which gives (XV) in a yield of 60 per cent. The dibromide (XX), m.p. 163–163·5° [infra-red spectrum ($CHCl_3$), 1741 cm^{-1} (ester and ketone), 1635 cm^{-1} (lactam)] in turn may be obtained by bromination of (XIII) in glacial acetic acid. In this bromination we believe that the bromine at C_8 is the first one to be introduced and consequently most certainly is *trans* to the C_4–C_9 bridge. A displacement of the bromine at C_8 with inversion of this asymmetric centre and an elimination of the bromine at C_6 then leads to (XV), which consequently must have the configuration indicated.

Treatment of the keto ester (XIII) with 1 mole of bromine in glacial acetic acid gave rise to the monobromide (XXI), m.p. 129–130° [infra-red spectrum in CCl_4, 1745 cm^{-1} (ester), 1725 cm^{-1} (ketone), 1650 cm^{-1} (lactam)]. Alkaline hydrolysis of (XXI) gave an uncharacterised oily material, which definitely on spectroscopic grounds did not contain even traces of compound (XIV). This finding enables us to place the bromine in the monobromide at C_8, since a bromine at C_6 would be certainly easily eliminated with the formation of the conjugated keto ester chromophore.

Thus the structure and configuration of the selenium dioxide oxidation product (XV) may be deduced from its alternate formation via the dibromide (XX). It is now of considerable importance for further confirmation of the peripheral structure of annotinine to demonstrate that the oxidation product (XVI) is indeed a C_8 epimer of (XV).

There are two independent pieces of evidence, both supporting this assignment. Compound (XVI) was reduced with zinc and acetic acid to the saturated ketol, $C_{17}H_{23}O_5N$ (XXII), m.p. 218° [infra-red spectrum, 1724 cm^{-1} (ester and ketone), 1630 cm^{-1} (lactam)]. Bromination of this compound, even with a very large excess of bromine in acetic acid, gave in good yield only the monobromide $C_{17}H_{22}O_5NBr$, m.p. 215–216° [infra-red spectrum, 1730 cm^{-1} (ester and ketone), 1642 cm^{-1} (lactam)]. On attempted further bromination, the monobromide was recovered unchanged. When this behaviour of the saturated ketol (XXII) is contrasted with the easy dibromination of (XIII), it is clear that the hydroxy group in (XXII) must be located at C_8.

The second piece of evidence is an exceedingly unusual reaction, which, nevertheless, in spite of its unprecedented type provides support for the structure (XVI). Reduction of (XVI) with sodium borohydride gave the diol $C_{17}H_{23}O_5N$, formulated as (XXIII), m.p. 249–250° [infra-red spectrum, 1723 cm^{-1} (ester), 1621 cm^{-1} (lactam)].

The two hydroxy groups in (XXIII) are assumed to be *trans* to explain the extremely slow uptake of periodic acid by this material. Compound (XXIII) was next treated with sodium methoxide in methanol under reflux with the expectation that a vinylogous β-elimination would convert it to (XIV). However, this reaction did not take place, probably because it is not favoured by the *cis* arrangement of the hydrogen at C_7 and

hydroxyl at C_8. Instead, an $\alpha\beta$-unsaturated ketone $C_{15}H_{19}O_2N$, m.p. 140·5–141·5° [ultra-violet, spectrum, shoulder 230 mμ (log ε 4); infra-red spectrum, 1687 cm^{-1} (ketone), 1623 cm^{-1} (lactam)], formulated as (XXV), was obtainable in a yield of about 10 per cent.

We believe that a reaction analogous to the isomerisation of (XVIII) into (XIII) must have taken precedence. This reaction is portrayed by the arrows in formula (XXIII) and would lead to the enol of (XXII). If this compound is attacked by a methoxide ion, the intermediate (XXIV) may form and decompose [as indicated by the arrows in (XXIV)] to give dimethyl carbonate and the conjugated ketone (XXV).

Since compound (XV) was available in somewhat larger quantities via the dibromide, it was selected for further oxidation studies. Significant results from all the methods tried were obtainable only on application of the ingenious periodate–permanganate method of Lemieux and von Rudloff.[8] The oxidation products were separated by partition chromatography on silica gel and formic and succinic acid were identified. It is clear that the formic acid must originate from C_6 and succinic acid from C_8, C_{10}, C_{11} and C_{12}. Thus, in spite of the fact that the larger fragment of the oxidation still remains oily, the two compounds identified complete together with the work described in this and the previous[1] communication a rigorous verification of the skeletal structures used in the present discussion [(XIII)–(XXIV)].

Further confirmatory evidence on the structure of the area between C_7 and C_5 was obtained as follows. Compound (XIII) gave a quantitative yield of a benzylidene derivative (XXVI), $C_{24}H_{27}O_4N$, m.p. 212–213° [ultra-violet spectrum, λ_{max} 295 mμ (log ε 4·28); infra-red spectrum, 1741 cm^{-1} (ester), 1696 cm^{-1} (ketone), 1648 cm^{-1} (lactam), 1610, 1570 cm^{-1}]. A spectroscopically entirely similar (see under "Experimental") but oily furfurylidene derivative was prepared and ozonised. Decomposition of the ozonide gave an amorphous acid, which readily decarboxylated and yielded the crystalline dicarboxylic acid (XXVII), m.p. 304°.

We shall next turn our attention to the study of the anhydro ester (VIII), the dehydrogenation of which to the quinolone acid (IX) provided us with the most important clue for the ultimate elucidation of the structure.

From the origin of the anhydro ester (VIII) it is safe to assume that the carbomethoxy group is in the more stable configuration. On the other hand, in the annotinine compounds encountered previously, the unnatural configuration of the carboxyl (i.e., *trans* to the C_4–C_9 bridge) was always far more stable.

It was consequently surprising that on alkaline hydrolysis of (VIII) two acids were obtained and separated by fractional crystallisation in roughly equal quantities.

It was demonstrated that these two acids are C_5 epimers. One of them (the anhydro acid) gave on treatment with diazomethane the anhydro ester (VIII), the other (the *iso*anhydro acid) gave an isomeric *iso*anhydro ester (XXVIII), which must be regarded as the C_5 epimer of (VIII). Treatment of (VIII) and (XXVIII) in methanol with sodium methoxide gave in both cases the same equilibrium mixture. The ratio of (VIII) to (XXVIII) in this equilibrium mixture estimated from infra-red spectra is about 15 : 1.

Thus in order to explain the formation of the anhydro and *iso*anhydro acids on alkaline hydrolysis of (VIII) in approximately equal quantities, one must assume that either the less stable ester is hydrolysed more rapidly or else that the acids in the anion

[8] R. U. Lemieux and E. von Rudloff. *Canad. J. Chem.* **33**, 1701 (1955).

form are equilibrated and that in this equilibrium the *iso*anhydro acid anion is more favoured than the *iso*anhydro ester in the ester equilibrium.

It is not easy to make predictions about the relative stabilities of (VIII) and (XXVIII), since in both C_5 epimers the carboxyl may assume the quasi-equatorial conformation and in both there are strong non-bonded interactions with the C_4–C_9 bridge and the C_3 hydrogen. As a matter of fact, (VIII) might be even more stable in the quasi-axial than the quasi-equatorial conformation. This is borne out by the finding that the anhydro acid [corresponding to the ester (VIII)] forms exceedingly easily the lactone (XIX), $C_{16}H_{18}O_3NCl$, m.p. 305° [ultra-violet spectrum, end absorption; infra-red spectrum, no OH band, 1792 cm^{-1} (lactone), 1668 cm^{-1} (lactam)]. The lactone (XXIX) may be easily converted into the anhydro ester (VIII) by mild-base catalysed β-elimination followed by diazomethane treatment of the resulting acid.

The next point that had to be established about the anhydro ester is the connexion with an authentically unrearranged annotinine derivative. Such a derivative was the acid (XXX) obtained by a vigorous Wolff–Kishner reduction of the keto ester (XIII).

The anhydro ester (VIII) gave on reduction with sodium amalgam in refluxing ethanol a mixture of the acids (XXXI) and (XXXII), which were separated by fractional crystallisation. They are C_5 epimers, since the methyl esters of (XXXI) and (XXXII) on treatment with sodium methoxide in methanol give the identical equilibrium mixture, as ascertained by infra-red spectroscopy.

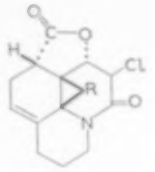
Vigorous hydrogenation of the high-melting acid (XXXII) with platinum oxide in glacial acetic acid gave the fully saturated acid (XXXIII). This compound was not identical with the acid (XXX). Moreover, esterification of (XXX) and (XXXIII) with diazomethane and equilibration of the esters with sodium methoxide in methanol resulted in non-identical equilibrium mixtures. The non-identity must be consequently due to the configuration at the asymmetric centre C_8.

If we assume that in the catalytic hydrogenation [(XXXII)→(XXXIII)], the hydrogen has been added *trans* to the C_4–C_9 bridge, then in the acid (XXX) the C_8 hydrogen must be *cis* to the C_4–C_9 bridge. Since the acid (XXX) was obtained from the ketone (XIII) in which the C_8 asymmetric centre is adjacent to a keto group, it follows that both (XIII) and (XXX) actually have the unnatural configuration at C_8 and that the keto ester (XIII) must have epimerised at C_8 in the course of the isolation, since it is stable to alkali.

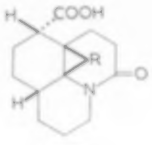
The finding that the configuration at C_8 as in (XXX) is more stable than as in (XXXIII) is not too surprising. First of all, we can deduce that the ring which originally carried the lactone must even after the opening of the lactone group remain in a quasi-chair form. If this was not the case and the ring changed into a quasi-boat, then in the boat form the natural configuration of the carboxyl would have become quasi-equatorial and more stable, which is contrary to experimental evidence.[1] If we now construct models of (XXX) and (XXXIII) with the carboxyl-carrying ring in a quasi-chair form, we see immediately that there is serious non-bonded interaction between the hydrogens of the C_4–C_9 bridge and the hydrogen at C_{10} in (XXXIII). This interaction makes (XXXIII) less stable than (XXX) in spite of the fact that in (XXX) C_{10} is quasi-axial with respect to the carboxyl-carrying ring.

This reasoning was finally corroborated and a correlation of (VIII) and (XXX) accomplished in the following manner. The methyl ester of (XXXII) was oxidised with selenium dioxide in glacial acetic acid to the oily acetoxy ester (XXXIV), which

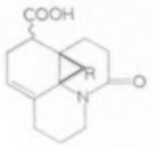
was saponified and one diastereoisomer of the hydroxy acid (XXXV), m.p. 275°, was isolated in crystalline form. Oxidation of (XXXV) with chromium trioxide in pyridine gave the amorphous keto acid (XXXVI) [ultra-violet spectrum, λ_{max} 236 mμ (log ε 3·99); infra-red spectrum (KBr pellet), 1705 cm^{-1} (ketone and carboxyl), 1635 cm^{-1} (lactam)].



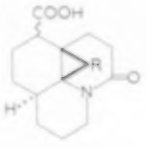
XXIX



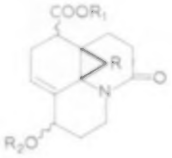
XXX



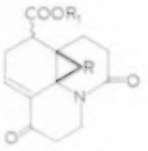
XXXI (m.p. 220°C)
XXXII (m.p. 271°C)



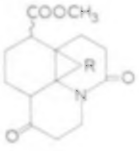
XXXIII



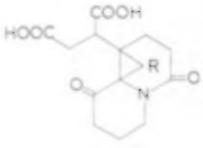
XXXIV ($R_1 = -CH_3$, $R_2 = -CO-CH_3$)
XXXV ($R_1 = H$, $R_2 = H$)
XXXVIII ($R_1 = -CH_3$, $R_2 = H$)



XXXVI ($R_1 = H$)
XXXVII ($R_1 = CH_3$)



XXXIX



XL, XLI

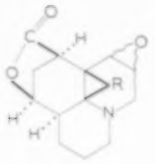
Compound (XXXVI) failed to decarboxylate on heating alone or on being heated under reflux with acid. This enables us to place the new substituent in (XXXVI), (XXXV) and (XXXIV) at C_{10}. Esterification of (XXXV) with diazomethane gave the oily methyl ester (XXXVII), which by oxidation (chromium trioxide–pyridine) gave the amorphous ester (XXXVIII) in good yield [ultra-violet spectrum, λ_{max} 236 mμ (log ε 3·94); infra-red spectrum, (CCl_4), 1740 cm^{-1} (ester), 1710 cm^{-1} (ketone), 1650 cm^{-1} (lactam)].

Hydrogenation of (XXXVIII) with palladium on calcium carbonate in alcohol gave a quantitative yield of the oily saturated keto ester (XXXIX) [ultra-violet spectrum, end absorption; infra-red spectrum, (CCl_4), 1735 cm^{-1} (ester), 1723 cm^{-1} (ketone), 1650 cm^{-1} (lactam); infra-red spectrum distinctly non-identical with keto ester (XIII)].

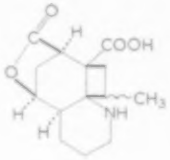
Compound (XXXIX), irrespective of the fact that it has been obtained via several oily intermediates, is derived directly from the anhydro ester (VIII). Moreover, (XXXIX) also has a ketone adjacent to the C_8 asymmetric centre and consequently, if our reasoning is correct, it should by a vigorous Wolff–Kishner reduction give the same product as the keto ester (XIII), that is the acid (XXX). This expectation was borne out by experiment. A Wolff–Kishner reduction of (XXXIX) gave a crystalline acid, which was identical by mixed melting point and infra-red spectrum with (XXX),

prepared by the Wolff–Kishner reduction of the keto ester (XIII). Thus it has been rigorously shown that the anhydro ester (VIII) is formed without any skeletal rearrangement.

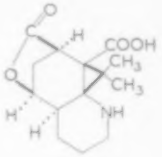
The only structural feature of the anhydro ester (VIII) that still possibly requires corroboration is the location of the double bond. This was achieved by applying the Lemieux oxidation[8] (periodate–permanganate) to the mixture of the two diastereoisomeric acids (XXXI) and (XXXII). It was possible to isolate from this oxidation by chromatography on silica gel two crystalline diastereoisomeric *seco*-keto acids (XL) and (XLI). The fact that they indeed are diastereoisomers follows rigorously from the finding that esterification with diazomethane and equilibration (sodium methoxide–methanol) convert both (XL) and (XLI) into the identical ester, as ascertained by infra-red spectroscopy.



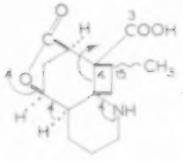
XLII



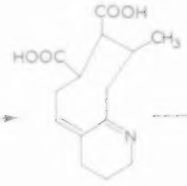
XLIV



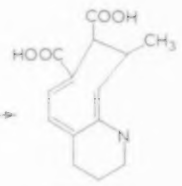
XLV



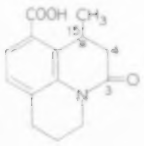
XLIII



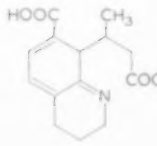
XLVII



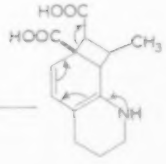
XLVIII



XLVI



L



XLIX

We have now shown that annotinine must be represented by the formula (XLII), in which the configuration of the oxide ring and the structure and configuration of the C_4–C_9 bridge remain to be determined. First of all, we wish to deal with the

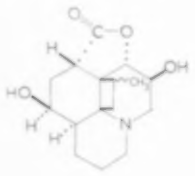
problem of the structure of the bridge R. It is obvious that (XLII) is a representation of three possible structural formulae. At the outset of our work[9] on annotinine we degraded this alkaloid to an amino acid $C_{14}H_{19}O_4N$, which according to the present discussion must be represented by (XLIII), (XLIV) or (XLV).

This amino acid was later subjected to a very mild dehydrogenation by Anet and Marion.[10] These authors have isolated an acid $C_{11}H_{15}O_3N$ as the major product of the dehydrogenation. We have later repeated the dehydrogenation and confirmed the properties of the dehydrogenation acid as reported by Anet and Marion. Moreover, we have succeeded to elucidate the structure of the dehydrogenation acid and to prove by synthesis that it has the formula (XLVI).[7]

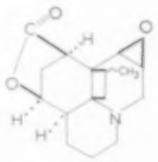
The dehydrogenation acid is optically active owing to the asymmetric carbon marked by an asterisk in (XLVI). It is clear that (XLVI) must have been formed by rearrangement from the amino acid represented by (XLIII), (XLIV) or (XLV). Of these structures, only (XLIII) has the correct arrangement of carboxyl and C-methyl to give rise to the lactam ring in (XLVI) with preservation of optical activity. Thus it can be seen that the carbons 3, 4 and 15 of (XLIII) form the lactam ring in (XLVI). From the several plausible ways to arrive from (XLIII) to (XLVI) we give only one, which does not necessarily represent the best pathway, but clearly demonstrates that of the three structures (XLIII), (XLIV) and (XLV) only (XLIII) may be converted to (XLVI) by an acceptable route.

The amino acid (XLIII) may be converted to (XLVII) by a reverse Mannich reaction, followed by β-elimination of the lactone ring. Dehydrogenation and tautomerisation of the imino group then give the *cyclo*octatriene derivative (XLVIII). The latter is converted to (XLIX) by transannular bridging and finally the new *cyclo*butane ring in (XLIX) is opened by a vinylogous reverse Mannich reaction and the product (L) is obtained. The conversion of (L) into the dehydrogenation acid (XLVI) does not require any comment.

The next point that may be clarified by a discussion of the reported behaviour of annotinine is the configuration of the oxide ring. We have shown previously[1] that annotinine hydrate, obtained by treatment of annotinine with alkali followed by acid,



LI



LII

has a new lactone ring formed between the epimerised carboxyl and hydroxy group at C_3, which has been generated by the opening of the oxide ring. Consequently, the structure of annotinine hydrate is portrayed by formula (LI). Since an intermediate oxido-hydroxy acid may be isolated[9] on shorter treatment with alkali, it becomes exceedingly probable that the actual opening of the oxide ring is performed by an intramolecular attack of the carboxylate ion. Consequently, we may represent

[9] D. R. Henderson, F. W. Stonner, Z. Valenta and K. Wiesner, *Chem. & Ind.* 544, 852 (1954).
[10] F. A. L. Anet and L. Marion, *Chem. & Ind.* 1232 (1954).

annotinine by the structure (LII), in which the configuration of the oxide ring is not proven but extremely probable and the configuration of the C-methyl group is unknown.

The confirmation of (LII) by X-ray crystallography in the National Research Council Laboratories in Ottawa[4] has finally revealed even this last point and shown that the methyl group is on the side of the lactone ring.

In the course of our work we have encountered a large number of rearrangement products that have no direct significance in the structural argument, but are interesting in themselves, as they illustrate the quite expected ability of annotinine to perform molecular acrobatics reminiscent of morphine chemistry.

We intend to report on some of these compounds in a separate communication.

EXPERIMENTAL

Anhydro ester (VIII). The hydroxy ester (VII)[1] (2 g) was heated under reflux for 2 hr with 2 g of phosphorus pentoxide on 100 ml of absolute xylene. The resulting solution was washed with water, dried and evaporated to dryness. From the oily product a 60 per cent yield of the anhydro ester (VIII) was obtained by direct crystallisation from light petroleum. After several crystallisations from the same solvent and from methanol, the sample melted at 159° and was sublimed for analysis (Found: C, 63·51; H, 6·13; N, 4·35; Cl, 11·23. Calc. for $C_{17}H_{20}O_3NCl$: C, 63·44; H, 6·26; N, 4·35; Cl, 11·02 per cent).

Dehydrogenation of the anhydro ester. The anhydro ester (VIII) (2 g) was thoroughly ground with 10% palladium on charcoal (1·5 g) and placed in a small bulb. A further 0·5 g of palladium on charcoal was spread over the mixture and the bulb was heated to 290–295° for 2 hr. The bulb with the contents was then ground up and extracted with ether in a continuous extractor. The acidic fraction was separated from this material and recrystallised to a constant m.p. of 286–286·5°; the yield was 0·22 g of the quinolone acid (IX) (Found: C, 68·22; H, 4·82. Calc. for $C_{13}H_{11}O_3N$: C, 68·11; H, 4·84 per cent). Ultra-violet spectrum, λ_{max} 236 (log ε 4·39), λ_{max} 283 mμ (log ε 3·77), λ_{max} 340 mμ (log ε 3·58). The rest of the material escaped dehydrogenation by subliming out of the bulb and was recovered.

The quinolone acid (IX) was further characterised by its methyl ester, which was prepared by treating (IX) with ethereal diazomethane. It crystallised from ether–light petroleum and melted constantly at 120–121° (Found: C, 68·66; H, 5·35; Calc. for $C_{14}H_{13}O_3N$: C, 69·11; H, 5·38 per cent). Infra-red spectrum, 1715, 1655, 1610, 1580 cm^{-1}.

Decarboxylation of the quinolone acid (IX). The acid (IX) (98 mg) was dissolved in quinolone (1 ml) and copper powder (80 mg) was added. The mixture was heated under reflux for 45 min, cooled, diluted with chloroform and washed three times with 20 per cent sulphuric acid, once with water, twice with 5 per cent sodium hydroxide, again with water, and then dried and evaporated to dryness. The residue was sublimed *in vacuo* at 100° with a cold finger. The sublimate (74 mg) was recrystallised to a constant melting point of 106–108°, which was not depressed on admixture of an authentic sample of 1-8-trimethylene-2-quinolone.[6] The infra-red spectra of the decarboxylation product and the authentic sample were identical in every detail.

Sodium amalgam reduction of the quinolone acid (IX). Acid (IX) (65 mg) was dissolved in ethanol (40 ml) and heated under reflux with stirring, while 15 g of

sodium amalgam (8% Na) was added over a period of 8 hr. The mixture was heated under reflux overnight. The alcohol solution was then decanted from the remaining amalgam and evaporated to a small volume *in vacuo*, and water was added. The solution was extracted with chloroform, acidified and again extracted with the same solvent. The yield was 46 mg of the dihydroquinolone acid (XI). After several crystallisations from methanol it melted at 266–267° (Found: C, 67·44; H, 5·73. Calc. for $C_{13}H_{13}O_3N$: C, 67·51; H, 5·67 per cent).

For infra-red spectroscopy the acid (XI) was converted to the methyl ester by treatment with ethereal diazomethane. The ester showed infra-red bands at 1728, 1665, 1605 and 1578 cm^{-1}.

Oxidation of keto ester (XIII) *with selenium dioxide*. The keto ester[1] $C_{17}H_{23}O_4N$, m.p. 200° (0·5 g), was dissolved in dioxan (12 ml) and a solution of selenium dioxide (0·25 g) in 12 ml of aqueous dioxan was added to it. The solution was heated under reflux with stirring for 16 hr and, after cooling, the precipitated selenium was filtered off. The solution was then evaporated to dryness, the residue was dissolved in chloroform and the solution was filtered through a column of neutral alumina (10 g). The oil thus obtained (0·6 g) was crystallised from acetone–ether to yield 124 mg of crystalline starting material. The mother liquors were chromatographed on neutral alumina (15 g). Benzene–ether (1 + 1) eluted 0·22 g of compound (XIV), which crystallised from ether in large blocks and melted after several crystallisations constantly at 144–145° (Found: C, 67·37; H, 6·93; N, 4·67. Calc. for $C_{17}H_{21}O_4N$: C, 67·31; H, 6·98; N, 4·62 per cent).

In a second experiment the keto ester (XIII) (1·35 g) was heated under reflux in 50 ml of dioxan with 1·35 g of selenium dioxide for 22 hr. Selenium was removed by filtration and the material was chromatographed on 25 g of acid-washed alumina.

The fractions eluted by benzene gave after several crystallisations from ether–light petroleum 80 mg of compound (XVII), which melted constantly at 127–128° (Found: C, 67·84; H, 6·52. Calc. for $C_{17}H_{19}O_4N$: C, 67·76; H, 6·35 per cent). Elution with benzene–ether (1 + 1) yielded 400 mg of the already described compound (XIV). Finally elution with chloroform–methanol (200 + 1) yielded 400 mg of oily material, from which compounds (XVI) and (XV) were separated by crystallisation from ethyl acetate and ether. Compound (XVI) was obtained pure in a yield of 0·19 g. It melted constantly at 246·5–247° (Found: C, 64·14; H, 6·67; N, 4·45; Calc. for $C_{17}H_{21}O_5N$: C, 63·93; H, 6·63; N, 4·39 per cent).

Compound (XV) was obtained in a yield of 70 mg and melted constantly at 212–213°. The mixed melting point and infra-red spectrum of this product were identical with compound (XV), obtained in good yield by hydrolysis of the dibromide (XX).

The dibromide (XX). The keto ester (XIII) (50 mg) was dissolved in glacial acetic acid (35 ml) and 0·5 ml of glacial acetic acid saturated with hydrogen bromide was added to it. A solution of 0·56 g of bromine in glacial acetic acid was added and it was decolorised in 6 hr. When more bromine was added, the solution remained brown indefinitely. The reaction solution was then poured into water and the precipitated dibromide was filtered off. After several recrystallisations from ethanol, it melted constantly at 163–163·5° (Found: C, 44·51; H, 4·71; Br, 32·24. Calc. for $C_{17}H_{21}O_4NBr_2$: C, 44·10; H, 4·58; Br, 34·51 per cent).

The monobromide (XXI). The keto ester (XIII) (0·67 g) was dissolved in 40 ml of acetic acid and glacial acetic acid (0·5 ml) freshly saturated with hydrogen bromide was added. Bromine (0·41 g) in 3 ml of acetic acid was then added and was decolorised in 40 min. The solution was poured into ice-water and the aqueous layer was extracted exhaustively with ether. The ether layer was washed with dilute bicarbonate solution and water and, after being dried, evaporated to dryness. The product (0·75 g) was recrystallised from methanol to a constant melting point of 129–130° (Found: C, 53·39; H, 5·80; Br, 20·87. Calc. for $C_{17}H_{22}O_4NBr$: C, 53·14; H, 5·77; Br, 21·77 per cent).

Hydrolysis of the dibromide (XX) *to compound* (XV). The dibromide (XX) (0·91 g) was dissolved in dioxan (25 ml) and 5 per cent aqueous potassium hydroxide (25 ml) was added. The resulting solution was heated under reflux for 1½ hr and cooled, and most of the solvent was removed *in vacuo*. Water was added and the aqueous solution was extracted with chloroform, acidified and continuously extracted with ether. The ether solution was dried, evaporated to a small volume, treated with ethereal diazomethane and evaporated to dryness. From the residue 288 mg of compound (XV) was obtained by crystallisation from benzene. After several crystallisations it melted constantly at 213° (Found: C, 64·11; H, 6·60. Calc. for $C_{17}H_{21}O_5N$: C, 63·93; H, 6·63 per cent).

Borohydride reduction of compound (XIV). Compound (XIV) (95 mg) was dissolved in methanol (5 ml) and 130 mg of sodium borohydride was added. The solution was kept at room temperature for 45 min and then treated as usual. Several crystallisations from ethyl acetate gave 56 mg of compound (XVIII), which melted at 235–236° (Found: C, 67·38; H, 7·59. Calc. for $C_{17}H_{23}O_4N$: C, 66·94; H, 7·60 per cent).

Isomerisation of (XVIII) *to* (XIII). Compound (XVIII) (35 mg) was heated under reflux overnight with 6 ml of 2 per cent methanolic sodium methoxide. The methanol was then removed *in vacuo* and water was added. The aqueous solution was extracted with ether, and the ether extract was dried and evaporated to dryness. The yield was 30 mg of brown oil, which was chromatographed on 1·2 g of neutral alumina. Elution with benzene–ether (1 + 1) gave 13 mg of a crystalline fraction. This material melted after two recrystallisations from acetone at 200° and was identical in infra-red spectrum and mixed melting point with compound (XIII).

The benzilidene derivative of (XIII). The keto ester (XIII) (100 mg) was dissolved in a solution of 60 mg of sodium in 10 ml of methanol. Benzaldehyde (0·1 g) was added and the solution was heated under reflux for 1 hr, cooled, concentrated and diluted with water. The remaining methanol was removed *in vacuo* and the aqueous solution was washed with chloroform and acidified. Extraction of the acidic solution with chloroform gave on evaporation of the chloroform 140 mg of a white foam. This material was esterified with diazomethane and recrystallised from ether to a constant melting point of 212–213° (Found: C, 73·20; H, 6·91; N, 3·71. Calc. for $C_{24}H_{27}O_4N$: C, 73·27; H, 6·91; N, 3·56 per cent).

The furfurylidene derivative of (XIII). The keto ester (XIII) (84 mg) was treated in exactly the same way as in the previous experiment, except that furfural (0·4 ml) was substituted for benzaldehyde. The endproduct after esterification was 0·15 g of a brown gum, which did not crystallise. It was chromatographed on 6 g of alumina. Chloroform eluted 0·1 g of a light yellow oil, which again did not crystallise. However, it exhibited the expected spectroscopic properties. Infra-red spectrum (CCl_4),

1742, 1697, 1652, 1607, 1540 cm^{-1}. Ultra-violet spectrum, λ_{max} (328 mμ (log ε 4·15).

Ozonolysis of the furfurylidene derivative. The oily furfurylidene derivative (0·73 g) was dissolved in ethyl acetate (100 ml) and cooled to −70°. Ozone was bubbled in at the rate of about 55 mg/min for 6 min, after which time the solution turned pale violet. The solution was warmed to room temperature and the ethyl acetate was removed by evaporation *in vacuo* below 20°. The oily residue was dissolved in glacial acetic acid (50 ml), and water (25 ml) concentrated hydrochloric acid (2 drops) and 30 per cent hydrogen peroxide (10 ml) were added. The resulting solution was stirred for 13 hr at room temperature and then the solvent was removed *in vacuo* below 50°. The residue was taken up in water and solid sodium bicarbonate was added until the solution became alkaline. The solution was then extracted with chloroform, acidified and extracted continuously with ether. The continuous extract gave 0·65 g of foam. This material was decarboxylated by being slowly heated up to 190° in a stream of nitrogen, which was then bubbled through a solution of barium hydroxide. The heating was discontinued when precipitation of barium carbonate has stopped. The residue (0·51 g) was chromatographed on a partition column of silica gel. The peak fraction 12, eluted with 5 per cent butanol in chloroform, contained 73 mg of the acid (XXVII) and was crystalline. It was recrystallised from acetone to a constant melting point of 302–304° (Found: C, 61·05; H, 7·12; Calc. for $C_{15}H_{21}O_5N$: C, 61·01; H, 7·17 per cent). The infra-red spectrum (KBr pellet) showed peaks at 1727 cm^{-1} (carboxyl) and 1600 cm^{-1} (lactam).

Hydrogenation of compound (XVII). Compound (XVII) (103 mg) was hydrogenated in 10 ml of glacial acetic acid with 50 mg of prehydrogenated platinum oxide for 12 hr. The product (XIX) was recrystallised from ether to a constant m.p. of 165–167°. A mixed melting point with the previously described[1] ester $C_{17}H_{25}O_4N$, m.p. 165–166° [compound (XX) in Valenta *et al.*[1]] showed no depression. Also the infra-red spectra of both materials were identical.

Borohydride reduction of (XVI). Compound (XVI) (470 mg) was reduced exactly in the same manner as described for compound (XIV). The product (XXIII) was obtained in a yield of 392 mg and was recrystallised to a constant m.p. of 249–250° from chloroform (Found: C, 63·55; H, 7·38. Calc. for $C_{17}H_{23}O_5N$: C, 63·48; H, 7·21 per cent). Ultra-violet spectrum, shoulder 210–220 mμ (log ε 4·0).

Compound (XXV). Compound (XXIII) (0·36 g) was dissolved in 50 ml of 2 per cent methanolic sodium methoxide and the solution was heated under reflux overnight. The methanol was taken to a small volume *in vacuo* and water was added. The aqueous solution was extracted several times with chloroform. Evaporation of the chloroform extracts to dryness gave 0·18 g of a colorless oil, from which 53 mg of starting material was obtained by crystallisation from chloroform. The mother liquors were chromatographed on 3·3 g of neutral alumina. Elution with benzene–ether (1 + 1) afforded 70 mg of a colorless oil, from which compound (XXV) crystallised on treatment with ether. It was recrystallised from ether–light petroleum to a constant m.p. of 140–141·5° (Found: C, 73·64; H, 7·79. Calc. for $C_{15}H_{19}O_2N$: C, 73·45; H, 7·81 per cent).

Zinc and acetic acid reduction of (XVI). Compound (XVI) (0·32 g) was dissolved in glacial acetic acid (50 ml) and heated to reflux temperature, and zinc dust (3 g) was gradually added to it. The heating was continued for 1½ hr, in the course of which time a second portion of zinc dust (3 g) was added. The remaining zinc dust was

filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up in water and extracted with chloroform. Evaporation of the chloroform gave 0·30 g of compound (XXII), which was recrystallised to a constant m.p. of 218° from methanol (Found: C, 63·62; H, 7·18. Calc. for $C_{17}H_{23}O_5N$: C, 63·52; H, 7·21 per cent).

Bromination of (XXII). Compound (XXII) (95 mg) was dissolved in glacial acetic acid (5 ml) and a few drops of acetic acid saturated with hydrogen bromide were added. Bromine (150 mg) was then added and the mixture was set aside for several hours. The reaction mixture was then diluted with water, bromine was decolorised by a few crystals of sodium sulphite and the aqueous solution was extracted with chloroform. The chloroform extract gave on evaporation to dryness 115 mg of the monobromo derivative, which was crystallised from ether to a constant m.p. of 215–216° (Found: C, 51·70; H, 5·50; Br, 21·53. Calc. for $C_{17}H_{22}O_5NBr$: C, 51·00; H, 5·54; Br, 19·96 per cent).

Periodate–permanganate oxidation of (XV). Compound (XV) was saponified by being heated on the steam-bath with 5 per cent methanolic potassium hydroxide for 6 hr. The crystalline acid was isolated in the usual way and used directly for the oxidation experiment. It was dissolved (1·6 g) in 1 M aqueous potassium hydroxide (6·5 ml) and aqueous potassium carbonate (400 ml of 0·02 M) was added to it. A solution of sodium metaperiodate (13·75 g) in water (300 ml) was added and the acidity was adjusted to pH 8 by addition of potassium hydroxide. After the addition of 0·2 g of potassium permanganate, the solution was kept at 30° for 30 hr. The reaction mixture was then acidified strongly with sulphuric acid and continuously extracted with ether. The ether was distilled off through a column and the residue was subjected to a short steam distillation. The distillate was again extracted with ether, the ether was removed and the residue was identified as formic acid by partition chromatography on a silica gel–water column according to Marvel and Rands.[11] The non-volatile portion from the steam distillation was extracted continuously with ether and the ether was evaporated to dryness. It yielded 1·06 g of a brownish gum. This material was subjected to partition chromatography on 320 g of silica gel. Only fractions 28 and 29, which are eluted with 20 per cent *n*-butanol in chloroform, crystallised. Recrystallisation from methanol–ethyl acetate gave 36 mg of material melting at 185–189°. This substance was crystallised until the constant m.p. of 197° was reached. This melting point showed no depression on admixture of authentic succinic acid. The infra-red spectra (taken in KBr pellets) of the oxidation product and authentic succinic acid were identical in every detail.

Saponification of the anhydro ester (VIII). The anhydro ester (VIII) (1·2 g) was heated under reflux for 2 hr with 5 per cent ethanolic potassium hydroxide. The hydrolysis mixture was worked up in the usual way and yielded 1·1 g of a crystalline acidic product. Crystallisation from ethyl acetate gave the crude anhydro acid (0·59 g), m.p. 285–290°. Recrystallisation of this material did not improve its purity, since the acid was on crystallisation spontaneously converted into the γ-lactone (XXIX). However, the anhydro acid was quantitatively converted by treatment with ethereal diazomethane into the anhydro ester (VIII) m.p. 159°. This latter compound was identified by mixed melting point and infra-red spectrum. Concentration of the mother liquors

[11] C. S. Marvel and R. D. Rands, Jr., *J. Amer. Chem. Soc.* 72, 2642, (1950).

gave a crop of the *iso*anhydro acid (0·40 g), which was recrystallised from benzene to a constant m.p. of 238–241° (Found: C, 62·39; H, 6·13; Cl, 11·44. Calc. for $C_{16}H_{18}O_3NCl$: C, 62·42; H, 5·89; Cl, 11·52 per cent).

The *iso*anhydro acid was converted into the *iso*anhydro ester (XXVIII) by treatment with ethereal diazomethane. This latter compound was recrystallised from ether–light petroleum to a constant m.p. of 142·5–143·5° (Found: C, 62·76; H, 5·99. Calc. for $C_{17}H_{20}O_3NCl$: C, 63·43; H, 6·26 per cent). Infra-red spectrum, 1735, 1660, 1630 cm^{-1}. The mixed m.p. with compound (VIII) was 120–125°.

Equilibration of (VIII) *and* (XXVIII). Each compound (VIII) and (XXVIII) (100 mg) was heated under reflux overnight with 15 ml of 2 per cent methanolic sodium methoxide. The solutions were evaporated *in vacuo* to a small volume, poured into ice-water and immediately extracted with chloroform. The esters thus obtained showed infra-red spectra identical in every detail.

Lactonisation of the anhydro acid. The anhydro acid (500 mg) was heated under reflux for 3 hr in absolute benzene (100 ml) containing 100 mg of toluene-*p*-sulphonic acid. The cooled reaction mixture was evaporated to a small volume and 150 ml of chloroform were added. The chloroform solution was washed with 5 per cent sodium carbonate and water, dried and evaporated to dryness. The crystalline lactone (XXIX) was obtained in a yield of 430 mg and it was recrystallised to a constant m.p. of 305° from chloroform (Found: C, 62·32; H, 5·92; Cl, 11·74. Calc. for $C_{16}H_{18}O_3NCl$: C, 62·42; H, 5·89; Cl, 11·52 per cent).

Conversion of the lactone (XXIX) *into the anhydro ester* (VIII). The lactone (XXIX) (90 mg) was dissolved in 5 per cent methanolic potassium hydroxide (10 ml) and heated under reflux for 30 min. The cooled solution was taken to a small volume, water was added, and the aqueous solution was extracted with chloroform. The aqueous layer was then cooled with ice, acidified with 10 per cent hydrochloric acid and extracted immediately with chloroform. The chloroform extract was dried and evaporated to dryness, and the residue was treated with ethereal diazomethane. Removal of the solvent and crystallisation from ether gave 70 mg of a compound m.p. 159°. It was identified by mixed melting point and infra-red spectrum as the anhydro ester (VIII).

Sodium amalgam reduction of the anhydro ester (VIII). The anhydro ester (VIII) 0·55 g) was dissolved in ethanol (100 ml) and treated at reflux temperature with 8% sodium amalgam for 23 hr. The solution was then decanted, evaporated to a small volume *in vacuo* and diluted with water. The aqueous solution was washed with chloroform, acidified and extracted with chloroform. Evaporation of the chloroform gave 0·54 g of crystalline acidic material, which was separated into the two epimeric acids (XXXI) and (XXXII) by fractional crystallisation from methanol–ether [compound (XXXI), m.p. 219–220° (Found: C, 69·91; H, 7·98); compound (XXXII), m.p. 270–271° (Found: C, 69·89; H, 8·00. Calc. for $C_{16}H_{21}O_3N$: C, 69·80; H, 7·69 per cent)]. Both acids were converted by treatment with ethereal diazomethane into the oily esters and these were equilibrated in the already described manner. Both acids (XXXI) and (XXXII) thus gave identical esters and ascertained by infra-red spectroscopy.

Catalytic hydrogenation of (XXXII). Compound (XXXII) (90 mg) was hydrogenated in glacial acetic acid over 50 mg of prehydrogenated platinum oxide. The uptake of hydrogen was finished in 6 hr and it was 90 per cent of the theory for 1 mole.

The hydrogenation mixture was worked up as usual and it yielded 80 mg of the perhydro acid (XXXIII). This compound was recrystallised to a constant m.p. of 256–257° from methanol–ether (Found: C, 69·37; H, 8·48. Calc. for $C_{16}H_{23}O_3N$: C, 69·28; H, 8·36 per cent).

Wolff–Kishner reduction of the ester (XIII). The keto ester (XIII), m.p. 200° (0·4 g), was reduced by the Barton modification of the Wolff–Kishner procedure.[12] The reaction mixture was poured into ice and water and washed with chloroform. The aqueous layer was then acidified and exhaustively extracted with chloroform. The extract on evaporation to dryness gave 0·33 g of semi-crystalline material, from which 83 mg of compound (XXX) crystallised on treatment with ether. It was recrystallised from ether and acetone to a constant m.p. of 271° (Found: C, 68·82; H, 8·01. Calc. for $C_{16}H_{23}O_3N$: C, 69·28; H, 8·36 per cent). Compound (XXX) was clearly not identical in melting point and mixed melting point with the isomeric acid (XXXIII). The non-identity of the two products was corroborated by the distinct differences in their infra-red spectra (KBr pellets). Both compounds (XXX) and (XXXIII) were esterified with ethereal diazomethane and the esters were equilibrated as described for compounds (VIII) and (XXVIII). The equilibrated esters thus obtained were clearly non-identical, as ascertained by infra-red spectroscopy.

The seco-*ketodicarboxylic acids* (XL) *and* (XLI). The crystalline mixture of the two epimeric acids (XXXI) and (XXXII) (1·38 g) was suspended in 50 ml of water and dissolved by dropwise addition of 5 per cent aqueous potassium hydroxide. A solution of potassium carbonate (2·1 g in 30 ml of water) and a solution of potassium metaperiodate (8·7 g) and potassium permanganate (0·11 g) in 400 ml of water were then added. The mixture was left at room temperature for 6 hr, after which time it was acidified by addition of sulphuric acid and continuously extracted with ether. The continuous extract gave on evaporation to dryness 1·12 g of a white foam, which was subjected to partition chromatography on 350 g of silica gel.[11] Fraction 11 was eluted with *n*-butanol–chloroform (1 + 10) and contained 195 mg of crystalline material. Fractional crystallisation of this material from a mixture of methanol and chloroform gave the two *seco* acids (XL) and (XLI) [(XL), m.p. 230° (Found: C, 59·49; H, 6·55); (XLI), m.p. 258° (Found: C, 59·37; H, 6·56; N, 4·36. Calc. for $C_{16}H_{21}O_6N$: C, 59·44; H, 6·55; N, 4·33 per cent)]. Both acids showed an ultraviolet spectrum typical of a keto group λ_{max} 302 mμ (log ε 1·7). Both acids (XL) and (XLI) were esterified with ethereal diazomethane. The ester of (XLI) was crystalline and it was recrystallised from ether to a constant m.p. of 123·5–124° (Found: C, 62·02; H, 7·15; N, 4·31; OCH_3, 18·42. Calc. for $C_{18}H_{25}O_6N$: C, 61·52; H, 7·17; N, 3·99; OCH_3, 17·66 per cent). The esters of (XL) and (XLI) were equilibrated as described for compounds (VIII) and (XXVIII). The infra-red spectra of the equilibrated esters were identical in every detail.

Conversion of the anhydro ester (VIII) *to the acid* (XXX). The mixture of the epimeric acids (XXXI) and (XXXII) obtained by sodium amalgam reduction of (VIII) (*vide supra*) was esterified by ethereal diazomethane and subjected to selenium dioxide oxidation. The esters (2·12 g) were heated in glacial acetic acid (135 ml) under reflux with (2·1 g) of selenium dioxide for 24 hr. The reaction mixture was then filtered and evaporated to dryness *in vacuo*. The residue was taken up in chloroform and

[12] D. H. R. Barton, D. H. Y. Ives and B. R. Thomas, *J. Chem. Soc.* 2056 (1955).

washed with water, and the chloroform layer was evaporated to dryness. The yield was 2·2 g of a dark brown foam, which was purified by chromatography on neutral alumina (80 g). Chloroform eluted 1·465 g of oily material. According to its infra-red spectrum (1730, 1628 cm^{-1}) and subsequent transformations, it was assumed to be essentially the acetoxy ester (XXXIV). The oily ester (XXXIV) was saponified by heating under reflux with 5 per cent ethanolic potassium hydroxide (20 ml) for 3 hr. The hydrolysis mixture was worked up as usual and a 96 per cent yield of the crude acid (XXXV) was obtained. This product was recrystallised to a constant m.p. of 275° from methanol–ethyl acetate (Found: C, 65·81; H, 7·25. Calc. for $C_{16}H_{21}O_4N$: C, 65·96; H, 7·27 per cent). The compound (XXXV) (70 mg) was oxidised with chromium trioxide (100 mg) in pyridine (2 ml). The mixture was shaken for 21 hr and the acidic oxidation product separated as usual. The yield was 47 mg of the keto acid (XXXVI), which was amorphous (for spectra: see p. 94). Esterification of (XXXV) with ethereal diazomethane gave the oily ester (XXXVII). This compound (2·25 g) was shaken for 1 hr with 2 g of chromium trioxide in 45 ml of pyridine. The mixture was then allowed to stand for 17 hr and the neutral oxidation products were isolated as usual and purified by chromatography on 60 g of neutral alumina. Benzene–ether (1 + 1) eluted 1·36 g of compound (XXXVIII), which did not crystallise (for spectra, see p. 94). Hydrogenation of (XXXVIII) in ethanol with prehydrogenated palladium on calcium carbonate as catalyst resulted in an uptake of 1 mole of hydrogen in 13 hr and it gave a quantitative yield of the saturated ketone (XXXIX). This compound remained also oily and had an infra-red spectrum (see p. 94) distinctly different from the keto ester (XIII). Equilibration of (XXXIX) with methanolic sodium methoxide did not produce a significant change in the infra-red spectrum. The oily compound (XXXIX) (717 mg) was reduced by the Barton modification of the Wolff–Kishner reaction exactly in the same manner as compound (XIII) (*vide supra*). The acidic reduction product isolated from the reaction mixture was a semi-crystalline brown material (672 mg), from which 330 mg of crystals were obtained on treatment with ether. The substance was recrystallised to a constant m.p. of 271° from a mixture of methanol and acetone (Found: C, 69·55, 69·23; H, 8·34, 8·56; N, 4·91, 4·84; Calc. for $C_{16}H_{23}O_2N$: C, 69·28; H, 8·36; N, 5·05 per cent). The melting point of the product was not depressed on admixture of compound (XXX) [obtained by the reduction of compound (XIII)]. The infra-red spectra (KBr pellets) of the product and of compound (XXX) were identical in every detail.

Acknowledgements—We thank Professor R. B. Woodward, Harvard, for several stimulating discussions concerning the dehydrogenation mechanism of our amino acid into the lactam carboxylic acid (XLVI). We also express our gratitude to the National Research Council, Ottawa, and Eli Lilly & Company, Indianapolis, Indiana, U.S.A., for financial support of these investigations.

Tetrahedron, 1958, Vol. 4, pp. 105–110. Pergamon Press Ltd., London

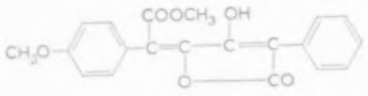
PREPARATION AND CONSTITUTION OF *ISO*PINASTRIC ACID

P. K. GROVER and T. R. SESHADRI
Department of Chemistry, Delhi University

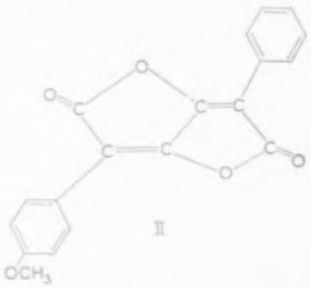
(*Received* 24 *February* 1958)

Abstract—In the synthesis of pinastric acid by Volhard's method the alcoholysis of 4-methoxypulvinic dilactone yields pinastric acid and an equal amount of an isomeric compound having the same chemical properties as pinastric acid and giving the same degradation products, but differing in physical properties and in the properties of the derivatives. The new compound is therefore a stereoisomer and is named *iso*pinastric acid. It seems to be the *trans–trans* form with reference to the 1 : 4-diphenylbutadiene system, pinastric acid being *cis–trans*. This interpretation is supported by the study of absorption spectra.

IN a recent publication (Mittal and Seshadri[1]) the isolation of pinastric acid from *Lepraria flava* was reported and a revised constitution (I) was suggested based on its reaction with *o*-phenylenediamine. With a view to studying this question more thoroughly, its synthesis was carried out by the method of Volhard.[2] 4-Methoxypulvinic dilactone (II) was obtained as an intermediate and it had all the properties recorded by Asano and Kamada.[3] When subjected to treatment with absolute methanolic potash or methanolic hydrochloric acid, a mixture of two products (in almost equal amounts) was obtained and not pinastric acid as reported by earlier



I



II

workers. The mixture could be separated by fractionation from methanol. The sparingly soluble first fraction, when crystallised from benzene, agreed in all its properties with naturally occurring pinastric acid (I), m.p. 202–204°. The more soluble second fraction had a much lower melting point, 120–121°, but had the same composition, two methoxyl groups and similar properties. Parallel study has been made of the derivatives of the two compounds; the carboxylic acids obtained by ester hydrolysis, the methyl ethers and acetates formed two different series. As compared with pinastric acid derivatives, the new series was characterised by lower melting points and higher solubility. But both the isomers, when hydrolysed and

[1] O. P. Mittal and T. R. Seshadri, *J. Chem. Soc.* 1734 (1956).
[2] J. Volhard, *Liebigs Ann.* **282**, 1 (1894).
[3] M. Asano and Y. Kamada, *Ber. Dtsch. Chem. Ges.* 67B, 1522 (1934).

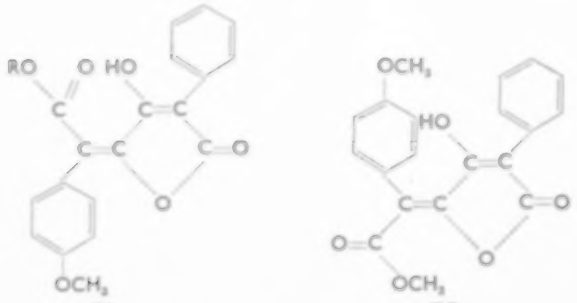
subjected to dehydration, yielded the same 4-methoxypulvinic dilactone (II). There is therefore no doubt that the two compounds are closely related.

In order to investigate if the isomerism was due to the difference in position of the nuclear methoxyl group, each of the isomers was condensed with *o*-phenylenediamine,[4] and the iminazole derivative obtained in each case was subjected to fission with potassium hydroxide; the same 4-methoxybenzylbenziminazole was formed. Hence it could be concluded that the nuclear methoxyl was attached to the same phenyl ring near to the ester group in both cases. It would therefore follow that the isomerism is stereoisomerism and hence the new low-melting isomer is named *iso*pinastric acid. More information about the isomer was provided by the following observations:

(1) Methylation of the dilactone (II) under mild conditions, the use of strong alkali being avoided, yielded only *iso*pinastric acid derivatives. With 1 mole of methyl sulphate and potassium carbonate in boiling acetone solution, a mixture of *iso*pinastric acid and its methyl ether was obtained, some of the dilactone remaining unchanged. With 2 moles of methyl sulphate the product was only *iso*pinastric acid methyl ether.

(2) *iso*Pinastric acid, when subjected to heat or heated with N-dimethylaniline or treated with absolute methanolic potash in the cold, underwent slow conversion into pinastric acid.

These observations are satisfactorily explained if *iso*pinastric acid (IIIb) is considered to be the *trans–trans* form of the 1:4-diphenylbutadiene system and pinastric acid (IV) to be the *cis–trans* form. This conclusion is supported by the ultra-violet absorption spectra (Fig. 1). The dilactone (*trans–trans*, II) and *iso*pinastric acid (IIIb) agree closely in the nature of the curves and positions of the maxima (270 and 310 mμ). Pinastric acid (*cis–trans*) has the maximum at a lower wavelength (295 mμ); as was earlier found in unsubstituted 1:4-diphenylbutadiene,[5] here also the lowering is 15 mμ. In the case of *trans*- and *cis*-stilbenes also the same difference is found. The infra-red spectra of the isomers do not have marked differences.



In contrast with unsubstituted 1:4-diphenylbutadiene in which the *trans–trans* form is the stablest under the influence of chemical catalysts, in the present case the

[4] O. P. Mittal and T. R. Seshadri, *J. Chem. Soc.* 3053 (1955).
[5] J. H. Pinkard, B. Wille and L. Zechmeister, *J. Amer. Chem. Soc.* **70**, 1938 (1948).

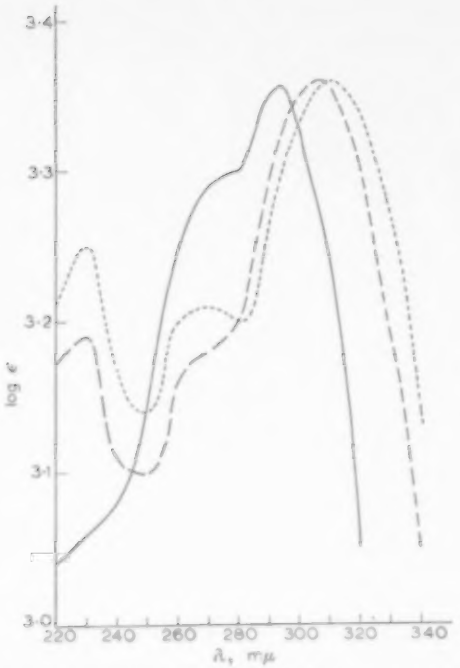
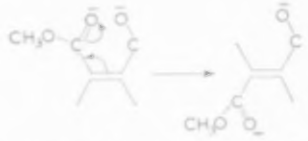
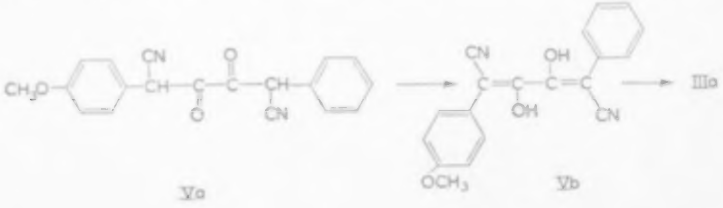


FIG. 1. Ultra-violet spectra in methanol solution; ——— pinastric acid; — — — *iso*pinastric acid; - - - - - - 4-methoxypulvinic dilactone.

cis–trans form seems to be somewhat more stable. This could be attributed to polar influences between the $—CO_2R$ and —OH groups, which may tend to repel each other and provide the driving force for the inversion. The mechanism can be represented as given below:



The change from *trans–trans* to *cis–trans* seems to be more easily effected under the conditions of the lactone ring fission by means of alcoholic potash or hydrochloric acid. In the course of this work the observation was made that 4-methoxydiphenylketipinic acid dinitrile (Va), prepared as an intermediate in the synthesis of 4-methoxypulvinic dilactone, yields on acid hydrolysis mostly 4-methoxypulvinic acid (*trans–trans* form) along with a small amount of the *cis–trans* form. This would indicate



Va Vb

that the *trans–trans* structure (Vb) of the dinitrile is probably the most stable and that isomeric change takes place only to a small extent in the course of the acid hydrolysis.

EXPERIMENTAL

Preparation of pinastric acid (IV) *and* iso*pinastric acid* (IIIb)

(i) 4-Methoxypulvinic dilactone (0·5 g) was dissolved in 2% absolute methanolic potash (150 ml) and the solution was allowed to stand for ½ hr. It was cooled in ice and acidified with dilute hydrochloric acid. The solid that separated was filtered off, dried and boiled with methanol and the solution was filtered. The undissolved portion crystallised from benzene as orange rectangular plates, m.p. 202–204°; the mixed m.p. with pinastric acid was undepressed. It agreed in all its properties with pinastric acid. The filtrate was concentrated, when a pale-orange coloured solid separated as fine needles (*iso*pinastric acid), m.p. 120–121° (Found: C, 68·3; H, 4·8; —OCH_3, 17·5. $C_{20}H_{10}O_6$ requires C, 68·2; H, 4·5; —OCH_3, 17·6 per cent). The two compounds were obtained in almost equal amounts.

(ii) The dilactone (0·5 g) was heated under reflux with methanol (25 ml) and hydrochloric acid (2 ml) for ½ hr. Methanol was removed under reduced pressure and water was added. The solid product was found to be the same as obtained in expt. (i) and the yields of the two acids were equal.

Carboxylic acid derivatives

(i) *Hydrolysis of* iso*pinastric acid.* *iso*Pinastric acid (0·1 g) was heated under reflux with 2% barium hydroxide (20 ml) for 10 min. The solution was cooled and acidified. The solid that separated was filtered off, dried and recrystallised from a mixture of ether and light petroleum (boiling range 40–60°) to yield orange coloured rectangular prisms of *trans–trans*-4-methoxypulvinic acid, m.p. 207–209° (Found: C, 67·8; H, 3·7; $C_{19}H_8O_6$ requires C, 67·5; H, 4·1 per cent). Hydrolysis of pinastric acid also gave a carboxylic acid having m.p. 207–209° (*cis–trans*). However, the mixed m.p. with the sample from *iso*pinastric acid was depressed (189–195°).

(ii) *Hydrolysis of* 4-*methoxydiphenylketipinic acid dinitrile*[3] (Va). The dinitrile (0·5 g), glacial acetic acid (5 ml), concentrated sulphuric acid (2 ml) and water (4 ml) were heated under reflux for 2 hr, cooled and diluted with water. The solid that separated was filtered off, dried and recrystallised from a mixture of chloroform and light petroleum (boiling range 40–60°), to give a product having m.p. 207–209°. It agreed in all its properties with the sample (*trans–trans*-carboxylic acid) obtained by the hydrolysis of *iso*pinastric acid with barium hydroxide; the mixed m.p. was undepressed.

The crude carboxylic acid obtained in the above described experiment (0·2 g), m.p. 172–184° was heated under reflux with acetone (20 ml), potassium carbonate (1 g) and dimethyl sulphate (0·03 ml, 1 mole) for 3 hr. After the potassium salts had been filtered off, acetone was distilled off from the filtrate and water was added to the residue. The solid product was treated with 5% aqueous sodium bicarbonate. The undissolved portion was dried and recrystallised from ethyl acetate and light petroleum (boiling range 40–60°) to yield yellow rhombohedral prisms (50 mg), m.p. 129–131°. The mixed m.p. with *iso*pinastric acid methyl ether was undepressed. The bicarbonate extract was acidified and the solid that separated was filtered off,

dried and boiled with methanol. A small amount that remained undissolved crystallised from benzene and light petroleum (boiling range 40–60°) as orange plates (15 mg), m.p. 202–204° (pinastric acid). The filtrate was concentrated, when orange coloured needles separated (70 mg), m.p. 120–121° (*iso*pinastric acid). The formation of *iso*pinastric (*trans–trans*) and pinastric (*cis–trans*) acids was therefore in the ratio of 8 to 1 and the yield of the *trans–trans* and *cis–trans* carboxylic acids should also have been in the same ratio.

The carboxylic acid (*trans–trans*) obtained by the ester hydrolysis of *iso*pinastric acid was heated under reflux with acetic anhydride (5 ml) for ½ hr. Acetic anhydride was removed under reduced pressure and the solid was recrystallised from benzene to yield yellow needles, m.p. 194–196°. The mixed m.p. with an authentic sample of 4-methoxypulvinic dilactone was undepressed.

VOL. 4 1958

iso*Pinastric acid methyl ether*

(i) *iso*Pinastric acid (0·1 g), acetone (20 ml), potassium carbonate (2 g) and excess of methyl iodide were heated under reflux for 3 hr. The solid product was dried and recrystallised from a mixture of ethyl acetate and light petroleum (boiling range 40–60°) to yield yellow thick rectangular prisms, m.p. 129–131° (Found: C, 68·6; H, 5·1; $C_{21}H_{18}O_6$ requires C, 68·8; H, 4·9 per cent). M.p. of pinastric acid methyl ether is 150–151°.

(ii) The carboxylic acid (*trans–trans*) (0·1 g) obtained by the two methods mentioned above, acetone (20 ml), potassium carbonate (2 g) and excess of methyl iodide were used and the product was worked up as described in (i) above. The yellow solid was dried and recrystallised from a mixture of ether and light petroleum (boiling range 40–60°) to yield yellow thick rectangular prisms, m.p. 129–131°. The mixed m.p. with the sample prepared as described in (i) was undepressed.

(iii) The dilactone when treated with 1 mole of dimethyl sulphate under the same conditions as mentioned below gave a mixture of *iso*pinastric acid and its methyl ether, some dilactone remaining unchanged. *iso*Pinastric acid was separated from the mixture with 5% aqueous bicarbonate. The methyl ether was separated from the dilactone by fractional crystallisation from ethyl acetate and light petroleum (boiling range 40–60°), when the methyl ether crystallised first and the dilactone later. 4-Methoxypulvinic dilactone (II) (0·2 g), acetone (40 ml), potassium carbonate (4 g) and dimethyl sulphate (2 moles, 1 ml) were heated under reflux for 3 hr. The product was crystallised from a mixture of ethyl acetate and light petroleum (boiling range 40–60°) to yield yellow stout rhombohedral prisms, m.p. 129–131° (Found: C, 68·7; H, 5·1; $C_{21}H_{18}O_6$ requires C, 68·8; H, 4·9 per cent).

iso*Pinastric acid acetate*

*iso*Pinastric acid (0·1g), acetic anhydride (5 ml) and two drops of dry pyridine were heated under reflux for ½ hr. The product was crystallised from ethyl acetate to yield yellow thin rectangular plates, m.p. 159–161°. The mixed m.p. with pinastric acid acetate (m.p. 170–171°) was considerably depressed (144–150°) (Found: C, 66·7; H, 4·7; $C_{22}H_{18}O_7$ requires C, 67·0; H, 4·6 per cent.)

Demethylation of iso*pinastric acid* (4-*acetoxypulvinic dilactone*)

*iso*Pinastric acid (0·5 g), glacial acetic acid (10 ml), hydriodic acid (2 moles, 1 ml) were heated under reflux at 140° for 5 hr. The mixture was cooled and poured over

crushed ice and extracted repeatedly with ether. The ether extract was washed first with water and then extracted with 5% sodium bicarbonate. The sodium bicarbonate extract was acidified, and the red solid obtained was collected, dried and heated under reflux with acetic anhydride (5 ml) for ½ hr. Acetic anhydride was removed under reduced pressure and the yellow solid was recrystallised from ethyl acetate to yield yellow stout rectangular prisms, m.p. 212–213°. Pinastric acid on similar treatment gave a yellow compound, m.p. 212–213°; the mixed m.p. with the above sample was undepressed.

Condensation of isopinastric acid with o-*phenylenediamine*

*iso*Pinastric acid (1 g), *o*-phenylenediamine (0·44 g) and N-dimethylaniline (36 ml) were heated at 200° in an oil bath for 4 hr. The mixture was cooled and poured over crushed ice containing hydrochloric acid. The brown solid was collected, dried and recrystallised from a mixture of ethyl acetate and light petroleum (boiling range 40–60°) to yield thin orange-red rectangular plates, m.p. 296–298° (Found: C, 73·3; H, 4·8; $C_{25}H_{18}O_4N_2$ requires C, 73·2; H, 4·4 per cent).

The above product (0·3 g) was heated under reflux with 15% absolute alcoholic potash (15 ml) for 5 hr. The colourless potassium salts that separated were filtered off. Alcohol was removed from the filtrate under reduced pressure and water was added. The colourless solid was collected, dried and recrystallised from a mixture of ethyl acetate and light petroleum (boiling range 40–60°), m.p. 165–167°. The mixed m.p. with an authentic sample of 4-methoxybenzylbenziminazole was undepressed.

Conversion of isopinastric acid into pinastric acid

(i) *iso*Pinastric acid (0·1 g) was heated in a test tube at 160° in an oil bath for 3 hr. The tube was cooled and the solid was boiled with methanol. The undissolved portion crystallised from a mixture of ether and light petroleum (boiling range 40–60°) as orange plates (yield 10 per cent), m.p. 202–204°; the mixed m.p. with pinastric acid was undepressed. Moreover it was observed that no dilactone was formed. *iso*Pinastric acid was recovered from the filtrate.

(ii) *iso*Pinastric acid (0·1 g) was dissolved in 2% absolute methanolic potash (50 ml) and the solution was kept in the cold for ½ hr. It was cooled in ice and acidified with dilute hydrochloric acid. The solid product was collected, dried and boiled with methanol. The undissolved portion crystallised from benzene as orange plates (yield 11 per cent), m.p. 202–204°. It agreed in all its properties with pinastric acid. *iso*Pinastric acid was recovered from the filtrate.

(iii) *iso*Pinastric acid (0·1 g) and N-dimethylaniline (11 ml) were heated at 180° in an oil bath for 3 hr. The mixture was cooled and poured over crushed ice mixed with hydrochloric acid. The pale-orange solid was washed first with cold dilute hydrochloric acid and then with cold water. The product dissolved completely in 5% sodium bicarbonate, showing that no dilactone was formed. It was also treated with hot methanol, and the undissolved portion crystallised as orange plates from benzene (yield 8 per cent), m.p. 202–204°. The mixed m.p. with pinastric acid was undepressed. The filtrate was concentrated, when *iso*pinastric acid crystallised out.

Acknowledgements—We thank Dr. K. Aghoramurthy and Dr. O. P. Mittal for help in the course of the work.

VOL. 4 195

Tetrahedron, 1958, Vol. 4, pp. 111–131. Pergamon Press Ltd., London

THE TRITERPENOIDS—LVI

THE CHEMISTRY OF THE SOYASAPOGENOLS A, B AND C

HUGH M. SMITH, JOHN M. SMITH and F. S. SPRING
The Royal College of Science and Technology, Glasgow

(*Received* 4 *March* 1958)

Abstract—Soyasapogenol A, B, and C are shown to be 3β:21:22:24-tetrahydroxyolean-12-ene, 3β:21α:24-trihydroxyolean-12-ene (XVIII) and 3β:24-dihydroxyoleana-12:21-diene (IX, R = H), respectively. Of the two possible configurations, α and β, for the *cis*-glycol group in soyasapogenol A the former is preferred, and soyasapogenol A tetra-acetate is represented by (X, R = Ac). The stereoisomeric soyasapogenol A tetra-acetate, which is obtained together with soyasapogenol A tetra-acetate by the oxidation of soyasapogenol C diacetate with osmium tetroxide, is consequently represented as 3β:21β:22β:24-tetra-acetoxyolean-12-ene (XI, R = Ac). Oxidation of soyasapogenol A tetra-acetate (X, R = Ac) and of the stereoisomeric soyasapogenol A tetra-acetate (XI, R = Ac) with selenium dioxide give the corresponding dioxodiene derivatives (XII) and (XVII), respectively. Treatment of each of the dioxodienes (XII) and (XVII) with alkali, and acetylation of the products, gives the same isomeric dioxodiene (XIII). These epimerisations include a reversed aldol-type condensation, followed by a direct intramolecular aldol-type condensation, and they prove that the *cis*-glycol group in soyasapogenol A is in ring É.

Soyasapogenol B (XVIII) forms a 3β:24-*iso*propylidene derivative (XIX), from which the 21-epimer of soyasapogenol B triacetate (XXII) is obtained by unambiguous procedures. Treatment of the dioxodiene derivative (XXIII) of the last compound with alkali, and subsequent acetylation, gives the dioxodiene derivative of soyasapogenol B triacetate (XXIV). This epimerisation again includes the opening and closing of ring É by a reversed aldol-type condensation and a direct intramolecular aldol-type condensation.

The identification of soyasapogenol B, which has been converted into soyasapogenol C, proves that the latter is 3β:24-dihydroxyoleana-12:21-diene (IX, R = H).

ACID hydrolysis of the saponin from soya bean gives a mixture from which four triterpenoid sapogenols, the soyasapogenols A, B, C and D, may be isolated.* Recently, soyasapogenols B and C, and possibly soyasapogenol A, have been obtained from a saponin mixture from ladino clover (*Trifolium repens*)[1] and soyasapogenol C has been isolated from whin (*Ulex europaeus*).[2] Preliminary studies by Japanese chemists* led to the views that the soyasapogenols are triterpenoids and contain a 1:3-glycol system similar to that in hederagenin; these views were confirmed and extended by Meyer *et al.*,[3] whose conclusions are summarised in the provisional formulae (I), (II), (III) and (IV) for soyasapogenols A, B, C and D, respectively. Meyer *et al.*, found that dihydrosoyasapogenol C, which is obtained by catalytic reduction of soyasapogenol C, is 3β:24-dihydroxyolean-12-ene, the reference specimen of which was prepared from α-boswellic acid. This incisive identification established the structure and stereochemistry of soyasapogenol C except for the position of the double bond susceptible to catalytic hydrogenation. The structure of soyasapogenol

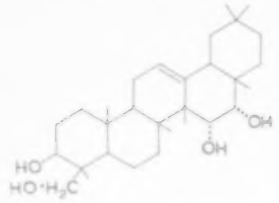
* References to early work on the soyasapogenols are listed in *Elsevier's Encyclopaedia of Organic Chemistry* (Ed. E. Josephy and F. Radt) Vol. 14, p. 592. Elsevier, New York and Amsterdam (1940). *Op. cit.* (Ed. F. Radt) Vol. 14–Supplement, p. 979 s. Elsevier, Amsterdam, Houston, London and New York (1952).

[1] E. D. Walter, E. M. Bichoff, C. R. Thompson, C. A. Robinson and C. Djerassi, *J. Amer. Chem. Soc.* **77**, 4936 (1955).

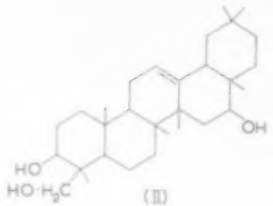
[2] J. McLean and J. B. Thomson, Unpublished work; we thank Dr J. McLean for this information.

[3] A. Meyer, O. Jeger and L. Ruzicka, *Helv. Chim. Acta* **33**, 672, 687, 1835 (1950).

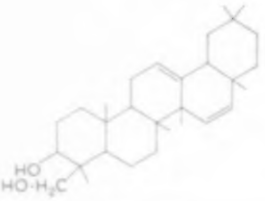
A follows from that of soyasapogenol C, since oxidation of the diacetate of the latter with osmium tetroxide, and acetylation of the product, gives soyasapogenol A tetra-acetate. The conversions, first, of soyasapogenol D and soyasapogenol C into a common derivative, and, secondly, of soyasapogenol B and soyasapogenol D into a common derivative, relate the position of the reactive double bond in soyasapogenol



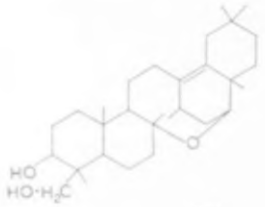
(I)



(II)



(III)



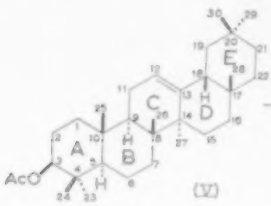
(IV)

C with the position of the isolated hydroxyl group in soyasapogenol B and with the position of one terminal of the oxide bridge in the tetracarbocyclic soyasapogenol D. In preliminary experiments, we converted soyasapogenol B into soyasapogenol C. Treatment of the former with acetone and sulphuric acid gives a 3β:24-*iso*propylidene derivative, which was dehydrated by reaction with phosphorus oxychloride and pyridine. Subsequent removal of the protecting *iso*propylidene group furnished soyasapogenol C, which was identified as its diacetate.

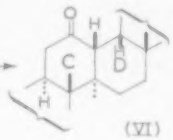
Meyer *et al.*[3] provided proof that the more reactive double bond in soyasapogenol C is of the type —CH=CH—, that this double bond is not located in ring A, and that the two double bonds in the sapogenol are not conjugated. Consequently, possible positions for the reactive double bond in soyasapogenol C are C_6–C_7, C_{15}–C_{16} and C_{21}–C_{22}, and the first of these was considered unlikely. In preliminary discussion, we designate the positions of the unlocated hydroxyl groups in soyasapogenol A as *x* and *y*.

Our interest in the soyasapogenols was aroused by the structure ascribed to soyasapogenol D by Meyer *et al.* and, as an essential prelude to a study of this compound, we undertook a further investigation of the soyasapogenols A, B and C. Our first objective was to test the structure (III) ascribed to soyasapogenol C. If this structure allocation is correct, soyasapogenol A must be 3β:15ξ:16ξ:24-tetrahydroxyolean-12-ene, e.g. (I), and to test this formula we applied to this sapogenol a series of reactions which involves ring D in an olean-12-ene derivative. Oxidation of β-amyrin acetate (V) with performic acid gives the saturated ketone, 12-oxo-oleanan-3β-yl acetate (VI), which reacts with bromine to furnish 12-oxo-olean-9(11)-en-3β-yl acetate (VII). Oxidation of this $\alpha\beta$-unsaturated ketone with selenium dioxide induces

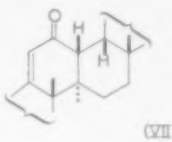
rearrangement with the formation of 12-oxotaraxera-9(11):14-dien-3β-yl acetate (VIII).[4] Oxidation of soyasapogenol A tetra-acetate, $C_{38}H_{58}O_8$ [24:x:y-triacetoxy derivative of (V)] with performic acid gives a saturated ketone, $C_{38}H_{58}O_9$ [24:x:y-triacetoxy derivative of (VI)]. Bromine converts this saturated ketone into an $\alpha\beta$-unsaturated ketone, $C_{38}H_{56}O_9$ [24:x:y-triacetoxy derivative of (VII)], which shows



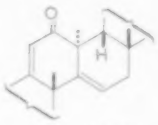
(V)



(VI)



(VII)



(VIII)

an intense ultra-violet absorption maximum at 2470 Å. Oxidation of the latter compound with selenium dioxide yields a tetra-acetoxy-12-oxotaraxera-9(11):14-diene, $C_{38}H_{54}O_9$ [24:x:y-triacetoxy derivative of (VIII)], which gives a yellow colour with tetranitromethane and shows an intense absorption maximum at 2440 Å. Alkaline hydrolysis of the tetra-acetoxy-oxodiene, $C_{38}H_{54}O_9$, furnishes the corresponding tetrahydroxy-oxodiene, $C_{30}H_{46}O_5$. Normal acetylation of the tetrahydroxy-oxodiene regenerates the tetra-acetoxy-oxodiene. That these reactions of β-amyrin acetate and of soyasapogenol A tetra-acetate are structurally analogous is confirmed by the comparison of molecular rotation differences in Table 1.

TABLE 1

β-Amyrin series	M_D	Δ	Soyasapogenol A series	M_D	Δ
3β-Acetoxyolean-12-ene (V)	+374°	−447°	3β:24:x:y-Tetra-acetoxy-olean-12-ene	+546°	−417°
3β-Acetoxy-12-oxo-oleanane (VI)	− 73	+367	3β:24:x:y-Tetra-acetoxy-12-oxo-oleanane	+129	+347
3β-Acetoxy-12-oxo-olean-9(11)-ene (VII)	+294	−486	3β:24:x:y-Tetra-acetoxy-12-oxo-olean-9(11)-ene	+476	−487
3β-Acetoxy-12-oxo-taraxera-9(11):14-diene (VIII)	−192		3β:24:x:y-Tetra-acetoxy-12-oxo-taraxera-9(11):14-diene	−11	

[4] J. Green, N. Mower, C. W. Picard and F. S. Spring, *J. Chem. Soc.* 527 (1944); O. Jeger and L. Ruzicka, *Helv. Chim. Acta* **28**, 209 (1945); G. G. Allen, J. D. Johnston and F. S. Spring, *J. Chem. Soc.* 1546 (1954).

The formation of tetra-acetoxy-12-oxotaraxera-9(11):14-diene [24:*x*:*y*-triacetoxy derivative of (VIII)] from soyasapogenol A tetra-acetate, and its recovery after alkaline hydrolysis and reacetylation, proves that the α-glycol system in soyasapogenol A cannot include C_{15} and C_{16}. Consequently the formulae (I), (II), (III) and (IV) cannot represent the structures of the soyasapogenols.

The proof that ring D is not the seat of the α-glycol system in soyasapogenol A focussed attention on ring E as the most likely alternative site.[3] To test this possibility, we attempted to prepare the 18α-isomer of soyasapogenol B, since 21- or 22- substituents equatorially bonded in an oleanane derivative become axially bonded in the 18α-oleanane isomer, and similarly 21- or 22- substituents axially bonded in an oleanane derivative become equatorially bonded in the derived 18α-oleanane isomer. We attempted to apply to soyasapogenol B triacetate the method used for the conversion of β-amyrin acetate into 18α-olean-12-en-3β-ol.[5] Oxidation of soyasapogenol B triacetate with chromium trioxide gave a mixture, m.p. 242–248°, from which pure 3β:24-*x*-triacetoxy-11-oxo-olean-12-ene could not be separated. Its ultra-violet absorption spectrum (λ_{max} 2480 Å, ε 6000) showed that this mixture contains an appreciable amount of the required αβ-unsaturated ketone, but chromatography and fractional crystallisation failed to purify this component. The mixture was treated with strong alkali in the hope that the αβ-unsaturated ketone would be inverted at C_{18}. Surprisingly, the product did not show any appreciable absorption in the neighbourhood of 2480 Å, but it did show strong absorption in the ethylenic region of the spectrum, from which we conclude that the αβ-unsaturated ketone component had been converted into a non-conjugated unsaturated ketone [11-oxo-13(18)-ene]. Acetylation of this product and chromatography of the acetate mixture yielded a saturated ketone as the only crystalline fraction. This ketone is 3β:24:*x*-triacetoxy-12-oxo-oleanane, the reference specimen of which we prepared by oxidation of soyasapogenol B triacetate with performic acid; this saturated ketone has been obtained by Tsuda and Kitagawa[6] by oxidation of soyasapogenol B triacetate with either chromium trioxide or hydrogen peroxide in acetic acid. Finally, the mixture, m.p. 242–248°, was treated with hydrochloric and acetic acids. The product, m.p. 285–300°, showed an absorption maximum at 2420 Å. The shift in the position of the absorption maximum indicated that the αβ-unsaturated ketone component had been converted into its 18α-isomer. The latter compound, however, could not be separated from the mixture either by fractional crystallisation or by chromatography. Consequently this route was abandoned.

We next prepared the 11:13(18)-dienes from soyasapogenol A and soyasapogenol B to determine whether the consequential change in the conformation of ring E is reflected in a change in the ease of esterification of the *x* and *y* hydroxyl groups. Soyasapogenol B is converted into its triacetate by treatment with pyridine and acetic anhydride at 5°. Oxidation of soyasapogenol B triacetate with selenium dioxide in acetic acid gives 3β:24:*x*-triacetoxyoleana-11:13(18)-diene, which shows the characteristic ultra-violet absorption spectrum of oleana-11:13(18)-dienes with intense maxima at 2410, 2490 and 2590 Å. Acetylation of the corresponding triol, using acetic anhydride and pyridine at 5°, regenerates the parent triacetate. The trihydroxydiene was characterised as its *iso*propylidine derivative, and oxidation of this compound

[3] R. Budziarek, W. Manson and F. S. Spring, *J. Chem. Soc.* 3336 (1951).
[6] K. Tsuda and S. Kitagawa, *Ber. Dtsch. Chem. Ges.* **71**, 790 (1938).

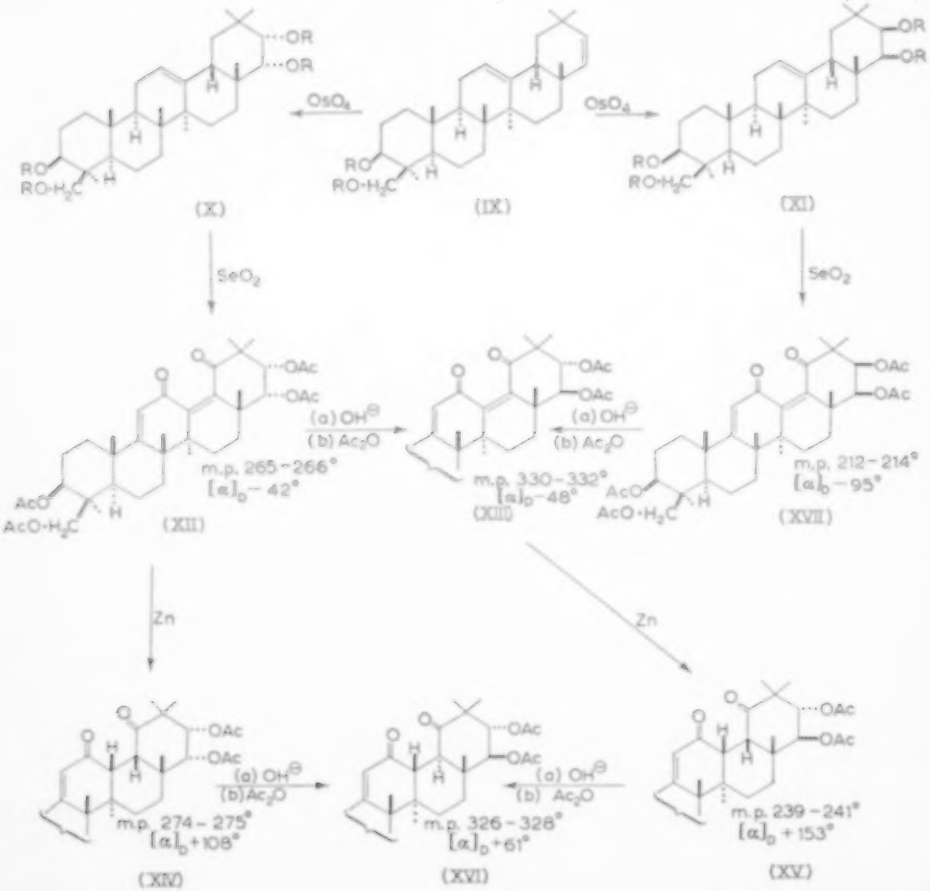
yielded *x*-oxo-3β:24-*iso*propylidenedioxyoleana-11:13(18)-diene. Acid hydrolysis of the protecting *iso*propylidene group and acetylation of the product furnished 3β:24-diacetoxy-*x*-oxo-oleana-11:13(18)-diene.

Oxidation of soyasapogenol A tetra-acetate with selenium dioxide in acetic acid yields 3β:24:*x*:*y*-tetra-acetoxyoleana-11:13(18)-diene. Acetylation of 3β:24:*x*:*y*-tetrahydroxyoleana-11:13(18)-diene, itself obtained by alkaline hydrolysis of the tetra-acetate, using acetic anhydride and pyridine at 5°, gave a mixture of a triacetate and the tetra-acetate. The triacetate is converted into the tetra-acetate by treatment with acetic anhydride and pyridine at 100°. Acetylation of soyasapogenol A, using acetic anhydride and pyridine at 5°, also gives a mixture of a triacetate and the tetra-acetate, and the former is converted into the tetra-acetate by hot acetylation. Oxidation of soyasapogenol A triacetate with selenium dioxide yields the triacetate of 3β:24:*x*:*y*-trihydroxyoleana-11:13(18)-diene, thus showing that the same hydroxyl group resists acetylation at 5° in both soyasapogenol A and in 3β:24:*x*:*y*-tetrahydroxyoleana-11:13(18)-diene. Although one interpretation of these reactions is that the α-glycol system in soyasapogenol A does not include C_{21} and C_{22}, an alternative explanation is that the method employed is not sufficiently delicate to detect the conformational change in ring E associated with the conversion of an olean-12-ene derivative into the related 11:13(18)-diene. That the latter is the correct explanation was shown by a study of the behaviour of 12:19-dioxo-9(11):13(18)-dienes derived from soyasapogenol A and soyasapogenol B.

Meyer *et al.* oxidised soyasapogenol A tetrabenzoate with selenium dioxide at 200° and obtained an amorphous oxidation product, which was not obtained crystalline after chromatography.[3] The amorphous product was hydrolysed by alkali, and the neutral product acetylated to give 3β:24:*x*:*y*-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene, m.p. 323–324°, $[\alpha]_D$ −48°, which shows the characteristic absorption spectrum of a 12:19-dioxo-oleana-9(11):13(18)-diene with a maximum at 2780 Å. We find that oxidation of soyasapogenol A tetra-acetate with selenium dioxide gives a different 3β:24:*x*:*y*-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene, m.p. 265–266°, $[\alpha]_D$ −42°, λ_{max} 2780 Å. When the tetra-acetoxy-dioxodiene, m.p. 265–266°, is hydrolysed with alkali and the product is acetylated, the higher melting isomer (m.p. 330–332°, $[\alpha]_D$ −48°, λ_{max} 2780 Å) is obtained. Since soyasapogenol A tetra-acetate is recovered unchanged after alkaline hydrolysis and acetylation of the product, the conversion of the tetra-acetoxy-dioxodiene, m.p. 265–266°, into the isomer, m.p. 330–332°, is supported by the 12:19-dioxo-9(11):13(18)-diene group or by part of this group, and this conversion is to be represented as a base-induced epimerisation of the groups attached to C_x and/or C_y. Now, 3β:24:*x*:*y*-tetra-acetoxy-12-oxo-olean-9(11)-ene [24:*x*:*y*-triacetoxy derivative of (VII)], prepared as described above, is recovered unchanged after hydrolysis with alkali and acetylation of the product, thus showing that the 12-oxo-9(11)-ene part of the dioxodiene chromophore is not in itself sufficient to support the base-induced epimerisation at C_x or C_y. That the 19- carbonyl is the activating group was shown as follows. Reduction of the tetra-acetoxy-dioxodiene, m.p. 265–266°, with zinc dust gives its 13β:18β-dihydro derivative, m.p. 274–275°, $[\alpha]_D$ +108°, λ_{max} 2440 Å. Similar reduction of the tetra-acetoxy-dioxodiene, m.p. 330–332°, gives its 13β:18β-dihydro derivative, m.p. 239–241°, $[\alpha]_D$ +153°, λ_{max} 2440 Å. Treatment of each of the isomeric dihydro derivatives with alkali and subsequent acetylation gives the same

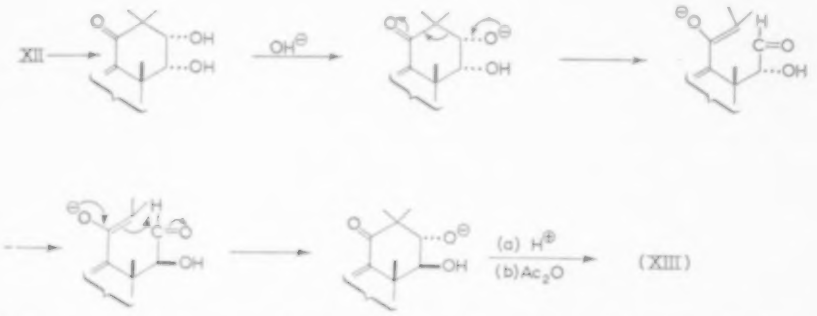
(third) isomeric dihydro derivative, m.p. 326–328°, $[\alpha]_D$ +61°, λ_{max} 2430 Å. A rational interpretation of these isomerisations requires that the *cis*-1:2-glycol system in soyasapogenol A includes C_{21} and C_{22} (X, R = H, or XI, R = H), from which it follows that soyasapogenol C is 3β:24-dihydroxyoleana-12:21-diene (IX, R = H).

Meyer *et al.*[3] showed that oxidation of soyasapogenol C diacetate with osmium tetroxide, followed by decomposition of the reaction product with sodium sulphite, and subsequent acetylation, gave a mixture from which soyasapogenol A tetra-acetate, a stereoisomeric soyasapogenol A tetra-acetate and the 11-oxo derivative of the last compound were isolated. The stereoisomer of soyasapogenol A tetra-acetate and its 11-oxo derivative were obtained in approximately 25 per cent total yield, and soyasapogenol A tetra-acetate in approximately 6 per cent yield. We have repeated the oxidation of soyasapogenol C diacetate with osmium tetroxide; the reaction product was decomposed with lithium aluminium hydride and acetylated. We isolated the stereoisomeric soyasapogenol A tetra-acetate in 30 per cent yield and soyasapogenol A tetra-acetate in 8 per cent yield. The method used by us for isolating the reaction products would convert the 11-oxo derivative of the epimeric



soyasapogenol A tetra-acetate into the corresponding 9(11):12-diene, and, although this compound was not isolated in a pure state, the presence of a 9(11):12-diene was confirmed by the ultra-violet spectra of later fractions from the chromatograph used for the separation of the two stereoisomeric tetra-acetates. Since soyasapogenol A is formed as a minor oxidation product of soyasapogenol C, and the stereoisomeric tetrol is the major product, the latter is probably formed by attack at the less hindered β-face, and the former by attack at the more hindered α-face of ring E. Consequently, we provisionally represent soyasapogenol A as 3β:21α:22α-24-tetrahydroxyolean-12-ene (X, R = H). Soyasapogenol A tetra-acetate is (X, R = Ac) and the stereoisomeric soyasapogenol A tetra-acetate is 3β:21β:22β-24-tetra-acetoxyolean-12-ene (XI, R = Ac). These steric assignments at 21 and 22, in our view, require a more stringent proof; although it may transpire that they are to be reversed, the interpretations given below would still be valid in principle.

The dioxodiene, m.p. 265–266°, obtained by direct oxidation of soyasapogenol A tetra-acetate is (XII) and the isomeric dioxodiene, m.p. 330–332°, is (XIII). The conversion of (XII) into (XIII) is represented as a reversed aldol-type condensation, followed by an intramolecular direct aldol-type condensation whereby a *cis*-(equatorial: axial) glycol diacetate group is converted into a *trans*-(di-equatorial) glycol diacetate group:



The dihydro derivative of the dioxodiene, m.p. 265–266°, is (XIV) and the dihydro derivative of the dioxodiene, m.p. 330–332°, is (XV). Treatment of (XV) with alkali inverts C_{18}, thereby giving, after acetylation, 3β:21α:22β:24-tetra-acetoxy-12:19-dioxo-18α-olean-9(11)-ene (XVI). In addition to inversion at C_{18}, treatment of (XIV) with alkali causes epimerisation at C_{22} by a reversed aldol: direct intramolecular aldol condensation sequence with the formation, after acetylation, of (XVI), the *cis*-(axial-equatorial) glycol diacetate group in (XIV) changing into a *trans*-(di-equatorial) glycol diacetate group.

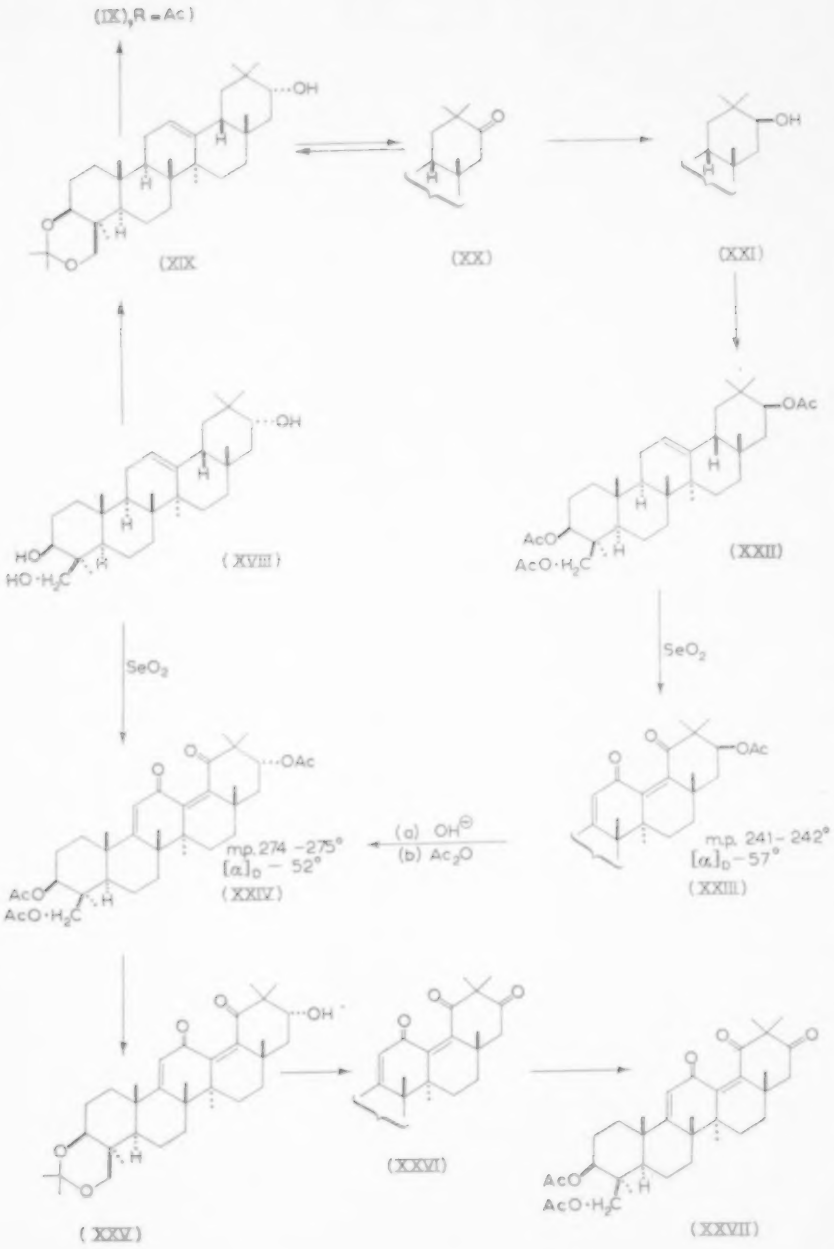
Confirmation of the general validity of the mechanism suggested for the conversion of the dioxodiene, m.p. 265–266°, into the isomer, m.p. 330–332°, was obtained as follows. Vigorous oxidation of the stereoisomeric soyasapogenol A tetra-acetate (XI, R = Ac) with selenium dioxide gives its dioxodiene derivative (XVII), m.p. 212–214°, $[\alpha]_D$ −95°, λ_{max} 2780 Å, which, after treatment with alkali and subsequent acetylation, yields the tetra-acetoxy-dioxodiene, m.p. 330–332° (XIII). This isomerisation is represented again as a reversed aldol: direct aldol condensation sequence, which, in this case, effects epimerisation of a *cis*-(axial-equatorial) glycol diacetate group to a *trans*-(di-equatorial) glycol diacetate group.

We next turn to a consideration of soyasapogenol B. Oxidation of soyasapogenol B triacetate with selenium dioxide gives 3β:24:*x*(or *y*)-triacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene, m.p. 274–275°, $[\alpha]_D$ −52°, which is converted into the corresponding trihydroxy-dioxodiene by alkaline hydrolysis.[3] Acetylation of the last-named compound regenerates the parent triacetoxy-dioxodiene, m.p. 274–275°, $[\alpha]_D$ −52°. Considered together with the established relationship between soyasapogenol C (IX, R = H) and soyasapogenol B, this behaviour suggests that the latter compound is either a 3β:22:24-triol, in which case the related dioxodiene is not a β-hydroxyketone and therefore not suceptible to a reversed aldol-type condensation, or that it is 3β:21α:24-trihydroxyolean-12-ene (XVIII), in which case the 21-hydroxyl group in the related dioxodiene is an equatorial substituent and will not epimerise with alkali. A decision was made between these alternatives in favour of the latter by the following experiments. Treatment of soyasapogenol B (XVIII) with acetone and sulphuric acid furnished the *iso*propylidene derivative (XIX), which was oxidised by the chromium trioxide–pyridine complex to the 21-ketone (XX). Reduction of this ketone with lithium aluminium hydride gave a mixture of stereoisomers, which was separated by chromatography into the 21α-hydroxy compound (XIX) and its 21β-epimer (XXI). Hydrolysis of the *iso*propylidene derivative (XXI) with mineral acid and acetylation of the product produced 3β:21β:24-triacetoxyolean-12-ene (XXII). Vigorous oxidation of (XXII) with selenium dioxide furnished the corresponding dioxodiene (XXIII), m.p. 241–242°, $[\alpha]_D$ −56·8°, λ_{max} 2800 Å. Treatment of (XXIII) with alkali and subsequent acetylation gave 3β:21α:24-triacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (XXIV), m.p. 274–275°, $[\alpha]_D$ −52°, identical with the product obtained by direct oxidation of soyasapogenol B triacetate with selenium dioxide. These experiments prove that the ring É hydroxyl group of soyasapogenol B is attached to C_{21} and that it is axially (α) bonded. In the derived dioxodiene triacetate (XXIV), the 21α-substituent is equatorially bonded and consequently alkali does not induce epimerisation. The 21-substituent in the epimer of soyasapogenol B triacetate (XXII) is equatorially bonded (β) and in the derived dioxodiene triacetate (XXIII) this substituent is axial. Consequently, when the dioxodiene triacetate (XXIII) is treated with alkali, a reversed aldol: direct aldol condensation sequence results in epimerisation to give, after acetylation, the 21α-(equatorial) acetate (XXIV).

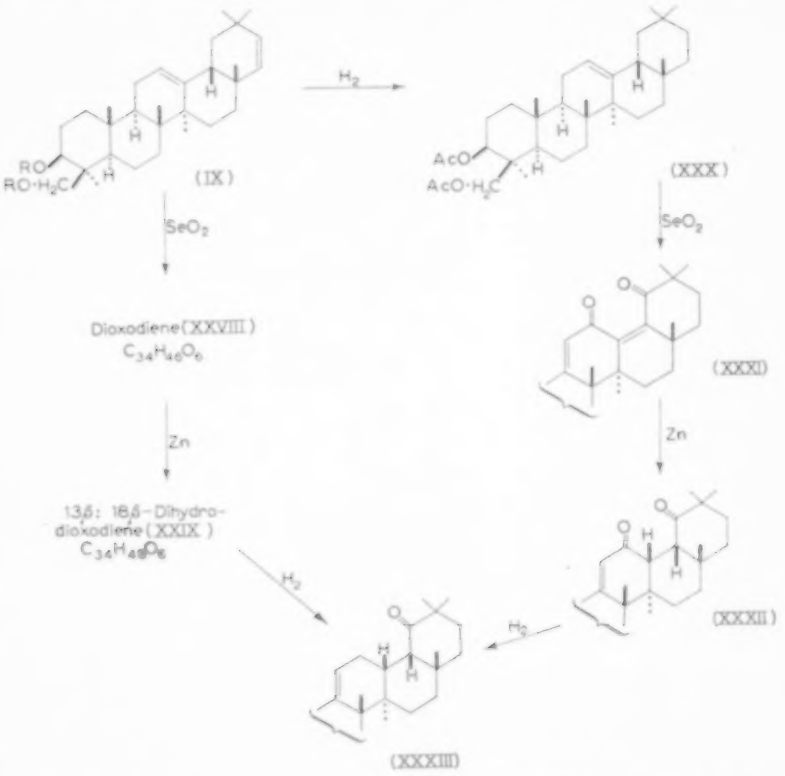
As stated above, the oxidation of soyasapogenol B triacetate with selenium dioxide gives the dioxodiene derivative (XXIV), hydrolysis of which with alkali gives the related triol now identified as 3β:21α:24-trihydroxy-12:19-dioxo-oleana-9(11)-:13(18)-diene. With acetone and sulphuric acid this triol forms its 3β:24-*iso*propylidine derivative (XXV), which when oxidised with the chromium trioxide–pyridine complex gives the 3β:24-*iso*propylidene derivative of the 12:19:21-trioxo-9(11):13(18)-diene (XXVI). Hydrolysis of the last-named compound with mineral acid and acetylation of the product gave 3β:24-diacetoxy-12:19:21-trioxo-oleana-9(11):13(18)-diene (XXVII). Attempts were made to hydrolyse this α:γ-diketone with alkali and with alkaline hydrogen peroxide; the alkali-soluble reaction products were not, however, obtained crystalline.

We record some related experiments with soyasapogenol C diacetate (IX, R = Ac). Vigorous oxidation of the diacetate with selenium dioxide gives a dioxodiene derivative (XXVIII), which, surprisingly, does not give a colour with tetranitromethane. Reduction of the 13:18-double bond in this dioxodiene derivative with zinc gave the

VOL. 4 1958


(IX), R = Ac)
OH
(XIX)
(XX)
OH
(XXI)
OH
HO
HO·H2C
(XVIII)
OAc
AcO
AcO·H2C
(XXII)
SeO2
SeO2
OAc
AcO
AcO·H2C
m.p. 274 -275°
[α]D - 52°
(XXIV)
(a) OH⊖
(b) Ac2O
OAc
m.p. 241 - 242°
[α]D - 57°
(XXIII)
OH
(XXV)
(XXVI)
AcO
AcO·H2C
(XXVII)

13β:18β-dihydro derivative (XXIX), which, again surprisingly, does not show isolated ethylenic absorption in the ultra-violet and does not give a colour with tetranitromethane. Vigorous oxidation of dihydrosoyasapogenol C diacetate (XXX) with selenium dioxide gives the dioxodiene derivative (XXXI), which is reduced by zinc to the 13β:18β-dihydro derivative (XXXII). Hydrogenolysis of 3β:24-diacetoxy-12:19-dioxo-olean-9(11)-ene (XXXII) gave 3β:24-diacetoxy-19-oxo-olean-9(11)-ene (XXXIII) and this ketone was also obtained by reduction of the dihydro-dioxodiene (XXIX) with hydrogen and platinum. In the latter case, hydrogenolysis of the 12-oxygen function is accompanied by reduction of the ring É double bond or its equivalent.



The identification of the soyasapogenols A, B, and C has a direct bearing upon the structure of soyasapogenol D. In particular, the identification of soyasapogenol B as 3β:21α:24-trihydroxyolean-12-ene (XVIII) shows that the oxide bridge in soyasapogenol D is attached to C_{21}. It is hoped to discuss the chemistry of this triterpenoid sapogenol in a later paper.

EXPERIMENTAL

M.p.'s are uncorrected. Rotations were measured in chloroform (unless otherwise stated) at 15–20°, and ultra-violet absorption spectra were measured in ethanol solutions. Grade II alumina and light petroleum, boiling range 60–80°, were used for chromatography.

Soya bean meal, which had been exhaustively extracted with light petroleum, was refluxed with boiling 80% alcohol and the extracted matter was hydrolysed successively with methanolic hydrochloric acid and with methanolic potassium hydroxide, essentially the method described by Meyer *et al.*[3] being used. A mixture of soyasapogenols and sterol was obtained from the alkaline liquor by extraction with benzene; approximately 10 g of this mixture was obtained from 3 kg of meal. The soyasapogenols were obtained from this mixture by using the preferred procedures described below; the physical constants of the sapogenols and their acetates observed by us are in good agreement with literature values. The sterol component of the mixture was identified as β-sitosterol.

Soyasapogenols A and B. The soyasapogenol–sterol mixture (65 g) was crystallised from benzene (650 ml) and the solid (25 g) was collected (mother liquor A) and acetylated with acetic anhydride and pyridine at 100°. A solution of the acetate mixture in light petroleum–benzene (5:1, 800 ml) was chromatographed on alumina (1 kg). Elution of the column with light petroleum–benzene mixtures (5:1, 5 l.; 4:1, 3 l.; 3:1, 4 l.) gave fractions which did not crystallise. Continued elution with light petroleum–benzene (1:1, 9·6 l.) gave crystalline fractions (total, 11 g), which were combined and crystallised from chloroform–methanol to yield soyasapogenol B triacetate as needles, m.p. 177–178°, $[\alpha]_D$ +79° (*c*, 1·2) (Found: C, 73·9; H, 9·8. Calc. for $C_{36}H_{56}O_6$: C, 73·9; H, 9·65 per cent). A solution of the triacetate in ether was refluxed with excess of lithium aluminium hydride for 1 hr and the product was crystallised from chloroform–methanol to give soyasapogenol B as needles, m.p. 260–261°, $[\alpha]_D$ +90° (*c*, 1·1).

A solution of soyasapogenol B (100 mg) in a cold mixture of acetic anhydride (5 ml) and pyridine (5 ml) was kept at 0–5° for 17 hr. Isolation of the product in the usual way gave soyasapogenol B triacetate (105 mg), as needles (from chloroform–methanol), m.p. and mixed m.p. 179–180°, $[\alpha]_D$ +77·5 (*c*, 1·0).

Continued elution of the alumina column with light petroleum–benzene (1:2, 16 l.), with benzene (12 l.) and with benzene–ether (20:1, 4 l.) gave fractions which crystallised with difficulty. Benzene–ether (10:1, 11 l.) then eluted crystalline fractions which were combined (total, 6·2 g) and recrystallised from chloroform–methanol to yield soyasapogenol A tetra-acetate as needles, m.p. 228–229°, $[\alpha]_D$ +85° (*c*, 1·0) (Found: C, 71·1; H, 9·1. Calc. for $C_{38}H_{58}O_8$: C, 71·0; H, 9·1 per cent). Hydrolysis of the tetra-acetate by boiling its solution in 3% methanolic potassium hydroxide for 3 hr gave soyasapogenol A as needles (from chloroform–methanol), m.p. 310–313°, $[\alpha]_D$ +103° (*c*, 0·5). Acetylation of soyasapogenol A by using acetic anhydride and pyridine at 100° regenerated the tetra-acetate as needles (from chloroform–methanol), m.p. and mixed m.p. 228–229°, $[\alpha]_D$ +85°.

Soyasapogenol D and β-sitosterol. The benzene mother liquor A (see above) was concentrated to half bulk. The amorphous solid (6·0 g) separating on standing was collected and acetylated by using pyridine and acetic anhydride at 100°, and a solution of the dry acetylated product in light petroleum–benzene (10:1, 1 l.) was chromatographed on alumina (180 g). Elution with light petroleum–benzene (10:1, 2 l.) gave amorphous fractions; continued washing with the same solvent mixture (9 l.) eluted crystalline fractions (total, 1·3 g), m.p.'s between 124° and 130°. These were combined and crystallised from chloroform–methanol to give β-sitosteryl acetate as plates, m.p. and mixed m.p. 128–129°, $[\alpha]_D$ −39·5° (*c*, 1·4). Alkaline hydrolysis of the acetate

and crystallisation of the product from chloroform–methanol gave *β*-sitosterol as needles, m.p. and mixed m.p. 135–136°, $[\alpha]_D$ −34° (*c*, 0·9).

Continued elution of the column with light petroleum–benzene (9:1, 2 l.; 4:1, 3·5 l.; 2:1, 2 l; 1:1, 4 l.) gave fractions (total 1·2 g) which after crystallisation from chloroform–methanol gave soyasapogenol D diacetate as plates, m.p. 191–192°, $[\alpha]_D$ −44° (*c*, 1·2) (Found: C, 75·3; H, 10·2. Calc. for $C_{34}H_{54}O_5$: C, 75·2; H, 10·0 per cent). Its infra-red spectrum (Nujol) includes a strong band at 1100 cm.$^{-1}$

A solution of the diacetate in ether was refluxed for 2 hr with an excess of lithium aluminium hydride and the product crystallised from chloroform–methanol to give soyasapogenol D as prisms, m.p. 297–299°, $[\alpha]_D$ −56·2° (*c*, 0·6).

Soyasapogenol C diacetate. The sapogenol–sterol mixture (60 g) was crystallised from methanol (200 ml). The separating solid (11 g) was recrystallised from benzene (150 ml). The solid was collected and the mother liquor was evaporated to dryness. The residue (6·5 g) was acetylated by using pyridine and acetic anhydride at 100°. A solution of the dry acetylated product in light petroleum–benzene (6:1, 500 ml) was chromatographed on alumina (250 g). After elution with light petroleum–benzene (6:1, 2 l.; 4:1, 1 l.), light petroleum–benzene (3:1, 4 l.) gave crystalline fractions (total, 1·4 g), which were combined and crystallised from chloroform–methanol to give soyasapogenol C diacetate as needles, m.p. 202–203°, $[\alpha]_D$ +59·5° (*c*, 1·3) (Found: C, 77·7; H, 10·2. Calc. for $C_{34}H_{52}O_4$: C, 77·8; H, 10·0 per cent).

Reactions of soyasapogenol A

3β:24-21α:22α-Bis-isopropylidenedioxy-olean-12-ene. A solution of soyasapogenol A (200 mg) in dry acetone (50 ml) and dry ether (200 ml) containing concentrated sulphuric acid (1 ml) was kept at 17° for 27 hr. The product was isolated in the usual way and purified by chromatography on alumina and crystallisation from chloroform–methanol to yield the *bis-isopropylidene derivative* as needles, m.p. 236–238°, $[\alpha]_D$ +93° (*c*, 1·5) (Found: C, 77·6; H, 10·6. $C_{36}H_{58}O_4$ requires C, 77·9; H, 10·5 per cent).

Soyasapogenol A triacetate. A solution of soyasapogenol A (130 mg) in a cold mixture of pyridine and acetic anhydride (1:1, 10 ml) was kept at 0–5° for 17 hr. The product was isolated in the usual way and its solution in light petroleum–benzene (2:1, 100 ml) was chromatographed on alumina (5 g). Elution with light petroleum–benzene (1:3, 7 × 150 ml) gave fractions (total, 85 mg) which crystallised from chloroform–methanol to yield soyasapogenol A tetra-acetate as needles, m.p. and mixed m.p. 228–230°, $[\alpha]_D$ +85° (*c*, 1·2). Further elution with benzene (500 ml), benzene–ether (20:1, 400 ml; 10:1, 500 ml; 4:1, 500 ml) gave fractions (total 45 mg) which crystallised from chloroform–methanol to yield *soyasapogenol A triacetate* as plates, m.p. 256–258°, $[\alpha]_D$ +71·7° (*c*, 0·8) (Found: C, 71·6; H, 9·3. $C_{36}H_{56}O_7$ requires C, 72·0; H, 9·4 per cent). Acetylation of the triacetate by using pyridine and acetic anhydride at 100° gave soyasapogenol A tetra-acetate as needles (from chloroform–methanol), m.p. and mixed m.p. 228–230°, $[\alpha]_D$ +83° (*c*, 0·6). Chromatography of soyasapogenol A tetra-acetate on the same preparation of alumina as that used for the separation of the triacetate gave an almost quantitative recovery of tetra-acetate.

Oxidation of soyasapogenol A tetra-acetate with performic acid. Soyasapogenol A tetra-acetate (1·0 g) in ethyl acetate (40 ml) was treated at 45° with a solution of

hydrogen peroxide (100 volume, 6·5 ml) in formic acid (99–100%, 34 ml) added dropwise over 3 hr. The solution was kept at 45° for 3 hr and then concentrated to one-third bulk. The crystals (750 mg) separating were recrystallised from chloroform–methanol, from which 3*β*:21*α*:22*α*:24-*tetra-acetoxy*-12-*oxo-oleanane* separated as needles, m.p. 308–310°, $[\alpha]_D$ +19·6° (*c*, 1·2) (Found: C, 69·1; H, 8·8. $C_{38}H_{58}O_9$ requires C, 69·3; H, 8·9 per cent). It does not give a colour with tetranitromethane in chloroform.

3*β*:21*α*:22*α*:24-*Tetra-acetoxy*-12-*oxo-olean*-9(11)-*ene*. A solution of bromine (0·38 g) in glacial acetic acid (25 ml) was added over 20 min to a solution of the saturated 12-ketone (1·4 g) in glacial acetic acid (100 ml) at 60–63°. The mixture was kept at 100° for 5 hr and at room temperature overnight. Water was added to the heated solution until crystals formed. After standing, the crystals (1·1 g) were collected and recrystallised from chloroform–methanol, from which 3*β*:21*α*:22*α*:24-*tetra-acetoxy*-12-*oxo-olean*-9(11)-*ene* separated as needles, m.p. 275–276°, $[\alpha]_D$ +72·6° (*c*, 1·0), λ_{max} 2470 Å (*ε* 11,000) (Found: C, 69·7; H, 8·4. $C_{38}H_{56}O_9$ requires C, 69·5; H, 8·6 per cent). It does not give a colour with tetranitromethane.

A solution of the tetra-acetoxy-*αβ*-unsaturated ketone (120 mg) in methanolic potassium hydroxide (3%, 30 ml) was refluxed for 2½ hr. The product was isolated by means of ether and acetylated by using pyridine and acetic anhydride at 100°. Crystallisation of the acetylated product from chloroform–methanol gave 3*β*:21*α*:22*α*-24-tetra-acetoxy-12-oxo olean-9(11)-ene as needles, m.p. and mixed m.p. 272–274°, $[\alpha]_D$ +72·9° (*c*, 1·1).

Oxidation of tetra-acetoxy-12-*oxo-olean*-9(11)-*ene with selenium dioxide*. Selenium dioxide (1·5 g) was added to a solution of the tetra-acetoxy-*αβ*-unsaturated ketone (900 mg) in glacial acetic acid (30 ml) and the mixture was heated under reflux for 24 hr. Water was added to the filtered solution, and the product was isolated by means of ether. It was purified by chromatography on alumina, and crystallisation from aqueous methanol gave 3*β*:21*α*:22*α*:24-*tetra-acetoxy*-12-*oxo-taraxera*-9(11):14-*diene* as plates, m.p. 240–241°, $[\alpha]_D$ −1·7° (*c*, 4·1). λ_{max} 2440 Å (*ε* 11,200 and $\varepsilon_{2\cdot80}$ 8000) (Found: C, 69·8; H, 8·4. $C_{38}H_{54}O_9$ requires C, 69·7; H, 8·3 per cent). It gives a pale yellow colour with tetranitromethane in chloroform.

3*β*:21*α*:22*α*:24-*Tetrahydroxy*-12-*oxo-taraxera*-9(11):14-*diene*. A solution of 3*β*:21*α*:22*α*:24-tetra-acetoxy-12-oxo-taraxera-9(11):14-diene (200 mg) in 3% methanolic potassium hydroxide was refluxed for 3 hr. The product was isolated by means of ether and crystallised from aqueous methanol to give the *tetrol* as prismatic needles, m.p. 296–298°, $[\alpha]_D$ −54·8° (*c*, 1·6 in methanol), λ_{max} 2440 Å (*ε* 11,000 and ε_{2080} 7500) (Found: C, 74·1; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5 per cent). Acetylation of the tetrol, using pyridine and acetic anhydride, gave the tetra-acetate as plates (from aqueous methanol), m.p. and mixed m.p. 240–241°, $[\alpha]_D$ −1·6° (*c*, 2·0).

Oxidation of soyasapogenol A tetra-acetate with selenium dioxide to 3*β*:21*α*:22*α*:24-*tetra-acetoxy-oleana*-11:13(18)-*diene*. Selenium dioxide (200 mg) was added to a solution of soyasapogenol A tetra-acetate (200 mg) in glacial acetic acid (30 ml) and the mixture was refluxed for 1 hr. The hot mixture was filtered and the product was isolated by means of ether and purified by chromatography on alumina and by crystallisation from chloroform–methanol to give 3*β*:21*α*:22*α*:24-*tetra-acetoxy-oleana*-11:13(18)-*diene* (150 mg) as needles, m.p. 242–243°, $[\alpha]_D$ +13·1° (*c*, 1·5), λ_{max} 2410, 2490 and 2590 Å (*ε* 30,000, 34,400 and 21,800) (Found: C, 71·2; H, 8·8.

$C_{38}H_{56}O_8$ requires C, 71·2; H, 8·8 per cent). Hydrolysis of the tetra-acetoxy-diene by refluxing its solution in 3% methanolic potassium hydroxide for 3 hr and crystallisation of the product from methanol gave 3β:21α:22α:24-*tetrahydroxyoleana*-11:13(18)-*diene* as plates, m.p. 322–324°, $[\alpha]_D$ −42·6° (*c*, 1·3 in ethanol), λ_{max} 2410, 2490 and 2590 Å (ε 30,000, 34,200 and 21,800) (Found: C, 76·15; H, 10·4. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2 per cent).

3β:21α:22α:24-*Tetrahydroxyoleana*-11:13(18)-*diene triacetate*. (a) A solution of the tetrahydroxy-diene in a mixture of pyridine and acetic anhydride (1:1, 10 ml) was kept overnight at 0–5°. The product, isolated in the usual way, was dissolved in light petroleum–benzene (2:1, 100 ml) and the solution was chromatographed on alumina (5 g). Elution with light petroleum–benzene (1:3, 5 × 130 ml) gave fractions (total 60 mg) which crystallised from chloroform–methanol to yield 3β:21α:22α:24-tetra-acetoxy-oleana-11:13(18)-diene as needles, m.p. and mixed m.p. 241–242°, $[\alpha]_D$ +13° (*c*, 1·0). Continued elution with ether and ether–methanol (20:1) gave fractions (total, 50 mg), which crystallised from chloroform–methanol to yield 3β:21α:22α:24-*tetrahydroxyoleana*-11:13(18)-*diene triacetate* as rods, m.p. 256–258°, $[\alpha]_D$ −10·5° (*c*, 1·1), λ_{max} 2420, 2500 and 2600 Å (ε 30,000, 34,200 and 21,900) (Found: C, 71·6; H, 9·3. $C_{36}H_{54}O_7$ requires C, 72·2; H, 9·1 per cent). Acetylation of the triacetate by using pyridine and acetic anhydride at 100° gave the tetra-acetate as needles (from chloroform–methanol), m.p. and mixed m.p. 241–242°, $[\alpha]_D$ +12° (*c*, 0·9). Chromatography of tetra-acetoxy-oleana-11:13(18)-diene on the same preparation of alumina as that employed for the separation of the triacetate gave a nearly quantitative recovery of the tetra-acetate.

(b) A solution of soyasapogenol A triacetate (70 mg) in glacial acetic acid (20 ml) was refluxed with selenium dioxide (70 mg) for 1 hr. The product was isolated by means of ether and its solution in light petroleum–benzene (1:1, 100 ml) was chromatographed on alumina (4 g). Elution with ether–methanol (20:1, 3 × 50 ml) gave fractions (total, 45 mg) which crystallised from chloroform–methanol to yield 3β:21α:22α:24-tetrahydroxyoleana-11:13(18)-diene triacetate as rods, m.p. and mixed m.p. 256–258°, $[\alpha]_D$ −9·0° (*c*, 0·5).

Oxidation of soyasapogenol A tetra-acetate (X, R = Ac) *with selenium dioxide to* 3β-21α:22α:24-*tetra-acetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XII). A solution of soyasapogenol A tetra-acetate (2·1 g) in benzyl acetate (30 ml) was refluxed with powdered selenium dioxide (2·1 g) for 24 hr. The filtered solution was evaporated to dryness under reduced pressure and the product was purified by chromatography on alumina and by crystallisation from chloroform–methanol to yield 3β:21α:22α:24-*tetra-acetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (850 mg) as needles, m.p. 265–266° $[\alpha]_D$ −42·5° (*c*, 1·0), λ_{max} 2780 Å (ε 13,600) (Found: C, 68·4; H, 8·0. $C_{38}H_{52}O_{10}$ requires C, 68·2; H, 7·8 per cent). It does not give a colour with tetranitromethane in chloroform.

3β:21α:22β:24-*Tetra-acetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XIII). A solution of 3β:21α:22α:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (100 mg) in methanolic potassium hydroxide (3%, 30 ml) was refluxed for 2½ hr. The product was isolated by means of ether and chloroform and acetylated by using acetic anhydride and pyridine. Crystallisation of the acetylated product from chloroform–methanol gave 3β:21α:22β:24-*tetra-acetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (75 mg) as prismatic needles, m.p. 330–332° (dec.), $[\alpha]_D$ −48·4° (*c*, 1·8), λ_{max}

2780 Å (ε 13,200) (Found: C, 68·0; H, 7·9. $C_{38}H_{52}O_{10}$ requires C, 68·2; H, 7·8 per cent). It does not give a colour with tetranitromethane in chloroform. A mixture with the isomeric 3β:21α:22α:24-tetra-acetate had m.p. 254°.

From the mother liquors of the dioxo-3β:21α:22β:24-tetra-acetate, unchanged 3β:21α:22α:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (10 mg), m.p. and mixed m.p. 263–267°, $[\alpha]_D$ −44° (*c*, 0·5), was isolated.

3β:21α:22α:24-*Tetra-acetoxy*-12:19-*dioxo-olean*-9(11)-*ene* (XIV). A solution of 3β:21α:22α:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (400 mg) in ethanol (50 ml) was refluxed with freshly activated zinc dust (4 g) for 5 hr. The product was isolated in the usual way and crystallised from chloroform–methanol to yield 3β:21α:22α:24-*tetra-acetoxy*-12:19-*dioxo-olean*-9(11)-*ene* (330 mg) as plates, m.p. 274–275°, $[\alpha]_D$ +108·4° (*c*, 1·5), λ_{max} 2440 Å (ε 12,100) (Found: C, 68·2; H, 8·3. $C_{38}H_{54}O_{10}$ requires C, 68·0; H, 8·1 per cent).

3β:21α:22β:24-*Tetra-acetoxy*-12:19-*dioxo-olean*-9(11)-*ene* (XV). 3β:21α:22β:24-Tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (310 mg) was reduced in ethanol with zinc dust as described above. The product was crystallised from chloroform–methanol to give 3β:21α:22β:24-*tetra-acetoxy*-12:19-*dioxo-olean*-9(11)-*ene* (220 mg) as blades, m.p. 239–241°, $[\alpha]_D$ +153·5° (*c*, 1·0), λ_{max} 2440 Å (ε 12,000) (Found: C, 68·2; H, 8·3. $C_{38}H_{54}O_{10}$ requires C, 68·0; H, 8·1 per cent).

3β:21α:22β:24-*Tetra-acetoxy*-12:19-*dioxo*-18α-*olean*-9(11)-*ene* (XVI). (a) A solution of 3β:21α:22α:24-tetra-acetoxy-12:19-dioxo-olean-9(11)-ene (150 mg) in aqueous methanolic potassium hydroxide (10%, 100 ml) was refluxed for 6 hr in an atmosphere of nitrogen. The product was isolated by means of chloroform and re-acetylated by treatment with pyridine and acetic anhydride for 16 hr at 15°. Crystallisation of the acetylated product from chloroform–methanol gave 3β:21α:22β:24-*tetra-acetoxy*-12:19-*dioxo*-18α-*olean*-9(11)-*ene* (110 mg) as needles, m.p. 326–328°, $[\alpha]_D$ +60·2° (*c*, 0·85), λ_{max} 2430 Å (ε 11,400) (Found: C, 68·0; H, 8·2. $C_{38}H_{50}O_{10}$ requires C, 68·0; H, 8·1 per cent).

(b) 3β:21α:22β:24-Tetra-acetoxy-12:19-dioxo-olean-9(11)-ene (87 mg) was treated with alkali in an atmosphere of nitrogen and the product was re-acetylated as described under (a) above. Crystallisation from methanol–chloroform yielded 3β:21α:22β:24-tetra-acetoxy-12:19-dioxo-18α-olean-9(11)-ene (60 mg) as needles, m.p. and mixed m.p. 326–328°, $[\alpha]_D$ +61° (*c*, 0·8), λ_{max} 2430 Å (ε 11,200).

When the isomerisations described under (a) and (b) were effected in air, and not in an atmosphere of nitrogen, the product was in each case contaminated with 3β:21α:22β:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene. For example, repetition of experiment (b) in air gave a product, m.p. 326–328°, $[\alpha]_D$ +39° (*c*, 1·0), λ_{max} 2440 (ε 10,000) and 2780 Å (ε 2000), which could not be resolved into its components by crystallisation.

Reactions of soyasapogenol B

Oxidation of soyasapogenol B triacetate with performic acid. Soyasapogenol B triacetate (1·0 g) was oxidised with performic acid by the method described for the oxidation of soyasapogenol A tetra-acetate. The product was crystallised from chloroform–methanol to yield 3β:21α:24-triacetoxy-12-oxo-oleanane (700 mg) as plates, m.p. 264–265°, $[\alpha]_D$ −44° (*c*, 3·1) (Found: C, 72·1; H, 9·3. Calc. for $C_{36}H_{56}O_7$: C, 72·0; H, 9·4 per cent). Tsuda and Kitagawa[6] give m.p. 254–256° for this keto-acetate.

A solution of the keto-acetate in 3% methanolic potassium hydroxide was refluxed for 3 hr, and the product was crystallised from aqueous methanol to yield 3β:21α:24-trihydroxy-12-oxo-oleanane as needles, m.p. 258–260°, $[\alpha]_D$ −10·2° (*c*, 1·5) (Found; C, 75·6; H, 10·3. Calc. for $C_{30}H_{50}O_4$: C, 75·9; H, 10·6 per cent). Tsuda and Kitagawa[6] give m.p. 253–254° for this keto-triol.

Oxidation of soyasapogenol B triacetate with chromium trioxide. A solution of soyasapogenol B triacetate (1·0 g) in glacial acetic acid (50 ml) was treated at room temperature with a solution of chromium trioxide (0·75 g) in water (0·7 ml) and acetic acid (7·5 ml) was added with stirring over 20 min. After 17 hr, the neutral product was isolated in the usual way and crystallised from chloroform–methanol to give plates (540 mg), m.p. 242–248°, $[\alpha]_D$ +30° (*c*, 2·0), λ_{max} 2480 Å (ε 6000). Attempts to separate the $\alpha\beta$-unsaturated ketone component of this mixture by careful chromatography, by fractional crystallisation and by fractional solution all failed. Oxidation of soyasapogenol B triacetate with chromium trioxide at 60° gave a similar inseparable mixture of saturated ketone and $\alpha\beta$-unsaturated ketone.

A solution of the mixture [m.p. 242–248°, λ_{max} 2480 Å (ε 6000), 340 mg] in 3% methanolic potassium hydroxide was refluxed for 6 hr. The product, a gum, did not show selective absorption near 2500 Å, but did show strong end absorption (ε_{2040} = 5000). The gum (310 mg) was acetylated by using pyridine and acetic anhydride, and a solution of the dry acetylated product in light petroleum–benzene (3:1, 50 ml) was chromatographed on alumina (10 g). Elution with benzene (200 ml) gave fractions (150 mg) which crystallised from chloroform–methanol to give 3β:21α:24-triacetoxy-12-oxo-oleanane as plates, m.p. and mixed m.p. 264–265°, $[\alpha]_D$ −4·4° (*c*, 1·2) (Found: C, 72·3; H, 9·3. Calc. for $C_{36}H_{56}O_7$: C, 72·0; H, 9·4 per cent).

A solution of the mixture (200 mg), m p. 242–248°, in acetic acid (20 ml) containing concentrated hydrochloric acid (2 ml), was heated on a steam-bath for 3 hr. The product crystallised from chloroform–methanol as plates, m.p. 285–300°, λ_{max} 2420 Å (ε 6000). The mixture could not be separated by crystallisation or by chromatography.

Oxidation of soyasapogenol B triacetate with selenium dioxide to 3β:21α:24-*triacetoxyoleana*-11:13(18) *diene.* A solution of soyasapogenol B triacetate (1·0 g) in glacial acetic acid (150 ml) was refluxed with selenium dioxide (1·0 g) for 1 hr. The product was isolated in the usual way and purified by chromatography on alumina and crystallisation from chloroform–methanol to yield 3β:21α:24-*triacetoxy-oleana*-11:13(18)-*diene* as needles, m.p. 250–251°, $[\alpha]_D$ −16·3° (*c*, 1·0), λ_{max} 2410, 2490 and 2590 Å (ε 30,000, 34 000 and 21,800) (Found: C, 74·0; H, 9·4. $C_{36}H_{54}O_6$ requires C, 74·2; H, 9·3 per cent). The triacetoxy-diene was hydrolysed by means of lithium aluminium hydride in ether. The trihydroxy-diene, which was not purified, was dissolved in a cold mixture of acetic anhydride and pyridine (1:1) and the solution was kept at 5° for 17 hr. The product was purified by chromatography on alumina and by crystallisation from chloroform–methanol to give the triacetoxy-diene as needles, m.p. and mixed m.p. 250–251°, $[\alpha]_D$ −16·1° (*c*, 1·0).

21α-*Hydroxy*-3β:24-iso*propylidenedioxyoleana*-11:13(18)-*diene.* A solution of 3β:21α:24-trihydroxyoleana-11:13(18)-diene (400 mg) in dry acetone (60 ml) and dry ether (300 ml) was treated with concentrated sulphuric acid (2 ml). After standing at 17° for 18 hr, the mixture was diluted with ether and washed with aqueous sodium hydrogen carbonate. The product was purified by chromatography on alumina and

crystallisation from chloroform–light petroleum to yield the *hydroxy*-iso*propylidene derivative* as plates, m.p. 235–236°, $[\alpha]_D$ −84° (*c*, 0·9) λ_{max} 2430, 2510 and 2600 Å (*ε* 29,000, 33,700 and 22,500) (Found: C, 79·8; H, 10·6; $C_{33}H_{52}O_3$ requires C, 79·8; H, 10·55 per cent).

21-*Oxo*-3*β*:24-iso*propylidenedioxyoleana*-11:13(18)-*diene*. The hydroxy-*iso*propylidene derivative (210 mg) was oxidised by treatment with the pyridine–chromium trioxide complex in the usual way. The product was purified by chromatography on alumina. Crystallisation from chloroform–light petroleum yielded 21-*oxo*-3*β*:24-iso*propylidenedioxyoleana*-11:13(18)-*diene* (170 mg) as rods, m.p. 243–245°, $[\alpha]_D$ −65° (*c*, 2·8), λ_{max} 2420, 2500 and 2590 Å (*ε* 25,800, 30,400 and 20,000). The infra-red spectrum includes bands at 1704 (carbonyl) and at 1155, 1105 and 1093 cm^{-1} (*iso*propylidenedioxy) (Found: C, 79·9; H, 10·2. $C_{33}H_{50}O_3$ requires C, 80·1; H, 10·2 per cent).

3*β*:24-*Diacetoxy*-21-*oxo*-*oleana*-11:13(18)-*diene*. A solution of the oxo-*iso*propylidene derivative (130 mg) in methanol (100 ml) containing concentrated hydrochloric acid (25 ml) was refluxed for 20 min. The product was isolated in the usual way and acetylated by treatment with acetic anhydride and pyridine at 100°. Crystallisation of the acetylated product from methanol gave 3*β*:24-*diacetoxy*-21-*oxo*-*oleana*-11:13(18)-*diene* (100 mg) as plates, m.p. 239–241°, $[\alpha]_D$ −33° (*c*, 0·8) λ_{max} 2420, 2520 (*ε* 30,000) and 2590 Å (Found: C, 75·6; H, 9·6. $C_{34}H_{50}O_5$ requires C, 75·8; H, 9·4 per cent). The infra-red spectrum (Nujol) includes bands at 1715 (carbonyl), 1736, 1266 and 1239 cm^{-1} (acetate).

Treatment of soyasapogenol B with acetone and sulphuric acid. A solution of soyasapogenol B (6·0 g) in dry ether (2 l.) and dry acetone (500 ml) containing sulphuric acid (20 ml) was kept at 17° for 60 hr. The mixture was diluted with ether and washed with aqueous sodium hydrogen carbonate. The product, isolated in the usual way, was purified by chromatography on alumina followed by crystallisation from aqueous methanol to give 21*α*-*hydroxy*-3*β*:24-iso*propylidenedioxyolean*-12-*ene* (XIX) as needles, m.p. 200–201°, $[\alpha]_D$ +73·6° (*c*, 2·2) (Found: C, 79·6; H, 10·9. $C_{33}H_{54}O_3$ requires C, 79·5; H, 10·9 per cent).

Conversion of soyasapogenol B (XVIII) *into soyasapogenol C* (IX, R = H). A solution of the *iso*propylidene derivative of soyasapogenol B (120 mg) in pyridine (20 ml) and phosphorus oxychloride (5 ml) was refluxed for 2 hr. The product was isolated by means of ether, and its solution in methanolic hydrochloric acid (2 N, 5 ml) was refluxed for 20 min. The crystalline product was isolated by using ether and acetylated by means of acetic anhydride and pyridine at 100°. The acetylated product was purified by chromatography on alumina and by crystallisation from chloroform–methanol to give soyasapogenol C diacetate (66 mg) as needles, m.p. and mixed m.p 200–201°, $[\alpha]_D$ +59° (*c*, 1·1). The infra-red spectrum of this specimen was identical with that of a specimen of soyasapogenol C diacetate isolated directly from soya bean.

Oxidation of 21*α*-*hydroxy*-3*β*:24-iso*propylidenedioxyolean*-12-*ene* (XIX). The complex prepared from chromium trioxide (3·0 g) and pyridine (30 ml) was added to a solution of the *iso*propylidene derivative of soyasapogenol B (3·0 g) in pyridine (30 ml) and the mixture was kept for 18 hr at 17° with occasional shaking. The product was isolated in the usual manner and its solution in light petroleum (300 ml) was chromatographed on alumina (100 g). Elution with the same solvent (2 l.) gave fractions which were combined and recrystallised from methanol to yield 21-*oxo*-3*β*:24-iso*propylidenedioxyolean*-12-*ene* (XX) (1·9 g) as prisms, m.p. 208–209°, $[\alpha]_D$

+14·3° (*c*, 0·9) (Found: C, 80·1; H, 10·7. $C_{33}H_{52}O_3$ requires C, 79·8; H, 10·55 per cent). The infra-red spectrum includes a strong band at 1703 cm^{-1}.

Reduction of 21-*oxo*-3β:24-iso*propylidenedioxyolean*-12-*ene* (XX) *with lithium aluminium hydride*. A solution of the ketone (1·8 g) in dry ether was refluxed with an excess of lithium aluminium hydride for 2½ hr. The product was isolated in the usual way and its solution in light petroleum (250 ml) was chromatographed on alumina (120 g). Elution with benzene (2·5 l.) gave fractions (total, 800 mg) which crystallised from methanol to yield 21α-hydroxy-3β:24-*iso*propylidenedioxyolean-12-ene as needles, m.p. and mixed m.p. 200–201°, $[\alpha]_D$ +73° (*c*, 1·1). Benzene (500 ml) and then benzene–ether (10:1, 2·5 l.) eluted fractions (800 mg) which crystallised from aqueous methanol as rosettes of needles, m.p. 127–140°. A solution of these fractions in light petroleum–benzene (1:1, 50 ml) was again chromatographed on alumina (70 g). Elution with light petroleum–benzene (1:9, 125 ml) gave a fraction (260 mg), m.p. 168–170°, $[\alpha]_D$ +70° (*c*, 0·6), which appeared to be a mixture. Continued elution with the same solvent mixture (1·8 l.) gave a fraction (500 mg), which after crystallisation from methanol yielded 21β-*hydroxy*-3β:24-iso*propylidenedioxyolean*-12-*ene* (XXI as needles, m.p. 128–130°, $[\alpha]_D$ +57·8° (*c*, 1·7) (Found: C, 79·3; H, 11·2 $C_{33}H_{54}O_3$ requires C, 79·5; H, 10·9 per cent). The infra-red spectrum includes a band at 3509 cm^{-1}.

3β:21β:24-*Triacetoxyolean*-12-*ene* (XXII). A solution of the 21β-hydroxy-*iso*propylidene derivative (500 mg) in methanol (150 ml) and concentrated hydrochloric acid (37·5 ml) was refluxed for 15 min. The mixture was diluted with water and the crystalline product was isolated by means of ether. The hydrolysis product was acetylated by treatment with acetic anhydride and pyridine for 48 hr at 17°. The acetylated product was isolated in the usual way and purified by chromatography on alumina and crystallisation from chloroform–methanol from which 3β:21β:24-*triacetoxy-olean*-12-*ene* separated as blades, m.p. 214–215°, $[\alpha]_D$ +64·5°(*c*, 2·5) (Found: C, 74·0; H, 9·7. $C_{36}H_{56}O_6$ requires C, 73·9; H, 9·65 per cent).

Vigorous oxidation of soyasapogenol B triacetate with selenium dioxide to 3β:21α:24-*triacetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XXIV). A solution of soyasapogenol B triacetate (1·8 g) in benzyl acetate (35 ml) was refluxed with powdered selenium dioxide (1·8 g) for 21 hr. The product was isolated in the usual way and purified by chromatography on alumina. Subsequent crystallisation of the product from chloroform–light petroleum and from chloroform–methanol gave 3β:21α:24-triacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (800 mg) as rods, m.p. 274–275°, $[\alpha]_D$ −52° (*c*, 2·5), λ_{max} 2780 Å (ε 12,800) (Found: C, 70·6; H, 8·5; Calc. for $C_{36}H_{50}O_8$: C, 70·8; H, 8·25 per cent). Meyer *et al.*[3] give m.p. 267·5–268° and $[\alpha]_D$ −48° for this compound.

3β:21α:24-*Trihydroxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene*. A solution of the dioxodiene triacetate (500 mg) in 3% methanolic potassium hydroxide (100 ml) was refluxed for 2½ hr. The product was isolated by means of chloroform and crystallised from aqueous methanol to give 3β:21α:24-trihydroxy-12:19-dioxo-oleana-9(11):13(18)-diene (405 mg) as plates, m.p. 301–303°, $[\alpha]_D$ −145° (*c*, 0·4 in pyridine), λ_{max} 2800 Å (ε 11,900). Meyer *et al.*[3] give m.p. 300–301°, $[\alpha]_D$ −145° (pyridine) for this compound. The triol was acetylated by using acetic anhydride and pyridine at 100° and the product was crystallised from chloroform–methanol to give 3β:21α:24-triacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene as rods, m.p. and mixed m.p. 273–274°, $[\alpha]_D$ −52° (*c*, 2·6), λ_{max} 2780 Å (ε 12,750.)

Vigorous oxidation of 3β:21β:24-*triacetoxyolean*-12-*ene* (XXII) *with selenium dioxide.* A solution of the triacetate (450 mg) in benzyl acetate (10 ml) was refluxed with selenium dioxide (400 mg) for 18 hr. The reaction product was isolated in the usual manner and purified by chromatography on alumina followed by crystallisation from chloroform–light petroleum to yield 3β:21β:24-*triacetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XXIII) as needles, m.p. 241–242°, $[\alpha]_D$ −56·8° (*c*, 1·1), λ_{max} 2800 Å (ε 12,600) (Found: C, 70·6; H, 8·1. $C_{36}H_{50}O_8$ requires C, 70·8; H, 8·25 per cent). A mixture with 3β:21α:24-triacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene had m.p. 230°.

Conversion of 3β:21β:24-*triacetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XXIII) *into* 3β:21α:24-*triacetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XXIV). A solution of the 3β:21β:24-triacetate (120 mg) in methanolic potassium hydroxide (3%, 100 ml) was refluxed for 2½ hr. Isolation by means of chloroform yielded a crystalline solid which was treated with pyridine and acetic anhydride at 100° for 1 hr. The acetylated product crystallised from chloroform–light petroleum to give 3β:21α:24-triacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (90 mg) as rods, m.p. and mixed m.p. 274–275° $[\alpha]_D$ −52·1° (*c*, 1·4), λ_{max} 2780 Å (ε 12,700).

Treatment of the dioxodiene derivative of soyasapogenol B with acetone and sulphuric acid. A solution of 3β:21α:24-trihydroxy-12:19-dioxo-oleana-9(11):13(18)-diene (380 mg) in dry acetone (50 ml) and dry ether (200 ml) containing concentrated sulphuric acid (2 ml) was kept at 17° for 60 hr. The product was isolated in the usual way and purified by chromatography. Crystallisation from light petroleum–chloroform gave 21α-*hydroxy*-12:19-*dioxo*-3β:24-iso*propylidenedioxyoleana*-9(11):13(18)-*diene* (XXV) (250 mg), as needles, m.p. 288–290°, $[\alpha]_D$ −77·3° (*c*, 1·2), λ_{max} 2800 Å (ε 12,000) (Found: C, 75·6; H, 9·4. $C_{33}H_{48}O_5$ requires: C, 75·5; H, 9·2 per cent).

12:19:21-*Trioxo*-3β:24-iso*propylidenedioxyoleana*-9(11):13(18)-*diene* (XXVI). Oxidation of the 21α-hydroxy-*iso*propylidene derivative (800 mg) with the pyridine–chromium trioxide complex, in the usual way, gave 12:19:21-trioxo-3β:24-iso*propylidenedioxy-oleana*-9(11):13(18)-*diene* (750 mg) as needles (from chloroform–light petroleum), m.p. 282–284°, $[\alpha]_D$ −208° (*c*, 1·1), λ_{max} 2800 Å (ε 13,;000) (Found C, 75·8; H, 9·1. $C_{33}H_{46}O_5$ requires C, 75·8; H, 8·9 per cent).

3β:24-*Diacetoxy*-12:19:21-*trioxo-oleana*-9(11):13(18)-*diene* (XXVII). The *iso*-propylidene derivative of the trioxodiene (750 mg) in methanol (100 ml) containing concentrated hydrochloric acid (25 ml) was refluxed for 15 min. The product was isolated by using ether and acetylated by treatment with acetic anhydride and pyridine at 100° for 3 hr. Crystallisation of the acetylated product from chloroform–light petroleum gave 3β:24-*diacetoxy*-12:19:21-*trioxo-oleana*-9(11):13(18)-diene (500 mg) as needles, m.p. 203–205°, $[\alpha]_D$ −131° (*c*, 2·3), λ_{max} 2800 Å (ε 12,000) (Found: C, 72·0; H, 8·4. $C_{34}H_{46}O_7$ requires C, 72·05; H, 8·2 per cent). Addition of methanolic potassium hydroxide (10%, 30 ml) to a methanol solution of the diacetoxy-trioxodiene (70 mg) gave a deep-orange solution. The solution was refluxed for 1 hr and then diluted with water. The product was not extracted from the alkaline solution by means of ether. Acidification of the aqueous solution with hydrochloric acid precipitated a solid, which was isolated by means of ether as an amorphous powder. Attempts to crystallise this acid and attempts to obtain a crystalline derivative by acetylation and by esterification with diazomethane all failed. Treatment of the amorphous acid with chloroform gives an intense blue solution.

Reactions of soyasapogenol C

Oxidation of soyasapogenol C diacetate (IX, R = Ac) *with osmium tetroxide.* Soyasapogenol C diacetate (850 mg) in pyridine (20 ml) was mixed with a solution of osmium tetroxide (0·6 g) in pyridine (6 ml) and the mixture was kept at 17° in the dark for 14 days. The mixture was diluted with ether (150 ml) and, after the addition of lithium aluminium hydride (2·0 g), refluxed for 1 hr. The product was isolated in the usual way and acetylated by means of acetic anhydride and pyridine. A solution of the acetylated product (900 mg) in light petroleum–benzene (10·1, 200 ml) was chromatographed on alumina (30 g). The column was washed successively with light petroleum–benzene mixtures (9:1, 320 ml; 6:1, 1120 ml; 7:3, 2720 ml; 3:2, 1280 ml; 2:3, 800 ml; 1:4, 320 ml) with benzene (800 ml) and finally with benzene–ether (3:1, 440 ml) to give fractions (50 × 160 ml). Evaporation of fractions 3–8 gave a solid (170 mg), which after crystallisation from chloroform–methanol furnished unchanged soyasapogenol C diacetate as needles, m.p. and mixed m.p. 203–204°, $[\alpha]_D$ +59°. Fractions 43–46 furnished soyasapogenol A tetra-acetate (70 mg) (X, R = Ac) as needles (from chloroform–methanol), m.p. and mixed m.p. 228–230°, $[\alpha]_D$ +89°. Fractions 9–42 were evaporated and the crystalline residues were combined (total, 600 mg) and rechromatographed on alumina (20 g). The column was washed successively with light petroleum–benzene mixtures (4:1, 800 ml; 3:7, 600 ml; 1:1, 1200 ml; 1:2, 1000 ml; 1:4, 2600 ml) with benzene (1 l.) and with benzene–ether (19:1, 2 l.) to give fractions (40 × 200 ml). Fractions 20–38 were evaporated and the combined solids (330 mg) were crystallised from chloroform–methanol to give 3β:21β:22β:24-tetra-acetoxyolean-12-ene (XI, R = Ac) as needles, m.p. 228–229°, $[\alpha]_D$ +41° (*c*, 1·1). Meyer *et al.*[3] give m.p. 226–227°, $[\alpha]_D$ +38°, for the stereoisomeric soyasapogenol A tetra-acetate. The crude solids obtained from fractions 16–33 showed selective absorption at 2800 Å (ε 1000). During recrystallisations, absorption at 2800 Å gradually diminished to $\varepsilon \simeq 50$.

Vigorous oxidation of the stereoisomeric soyasapogenol A tetra-acetate (XI, R = Ac) *with selenium dioxide.* A solution of 3β:21β:22β:24-tetra-acetoxyolean-12-ene (300 mg) in benzyl acetate (10 ml) was refluxed for 24 hr with selenium dioxide (250 mg). The product was isolated in the usual way and purified by chromatography on alumina and crystallisation from chloroform–methanol to give 3β:21β:22β:24-*tetra-acetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XVII) (150 mg) as prisms, m.p. 212–214°, $[\alpha]_D$ −95° (*c*, 0·9), λ_{max} 2780 Å (ε 13,000) (Found: C, 68·4; H, 7·6. $C_{38}H_{52}O_{10}$ requires C, 68·2; H, 7·8 per cent).

3β:21α:22β:24-*Tetra-acetoxy*-12:19-*dioxo-oleana*-9(11):13(18)-*diene* (XIII). A solution of 3β:21β:22β:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (100 mg) in methanolic potassium hydroxide (3%, 30 ml) was refluxed for 2½ hr. The product was isolated in the usual way and acetylated by means of acetic anhydride and pyridine at 100°. The acetylated product was crystallised from chloroform–methanol to give 3β:21α:22β:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (40 mg) as prisms, m.p. and mixed m.p. 330–332° (dec.), $[\alpha]_D$ −48° (*c*, 0·6), λ_{max} 2780 Å (ε 13,200). From the chloroform–methanol mother liquor, unchanged 3β:21β:22β:24-tetra-acetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (40 mg) was isolated, m.p. and mixed m.p. 210–212°, $[\alpha]_D$ −95·4° (*c*, 0·95).

Vigorous oxidation of soyasapogenol C diacetate (IX, R = Ac) *with selenium dioxide.* A solution of soyasapogenol C diacetate (250 mg) in benzyl acetate was

refluxed with powdered selenium dioxide (300 mg) for 18 hr. The product was purified by chromatography, followed by crystallisation from light petroleum–chloroform, from which the *dioxodiene* derivative separated as needles, m.p. 217–218°, $[\alpha]_D$ −78·5° (*c*, 0·8), λ_{max} 2740 Å (ε 12,500) (Found: C, 74·2; H, 8·5. $C_{34}H_{46}O_6$ requires C, 74·15; H, 8·4 per cent). The dioxodiene derivative does not give a colour with tetranitromethane in chloroform.

Reduction of the dioxodiene derivative of soyasapogenol C diacetate. The dioxodiene derivative (70 mg) in ethanol (10 ml) was refluxed with freshly activated zinc dust (1 g) for 5 hr. The product was isolated in the usual way and crystallised from chloroform–methanol, from which the dihydro derivative (45 mg) separated as plates, m.p. 266–268°, $[\alpha]_D$ +106° (*c*, 0·8), λ_{max} 2450 Å (ε 12,600) (Found: C, 74·0; H, 8·9. $C_{34}H_{48}O_6$ requires C, 73·9; H, 8·75 per cent). The dihydro derivative does not give a colour with tetranitromethane in chloroform.

The dihydro derivative (30 mg) in acetic acid (50 ml) was shaken with hydrogen and platinum (from 250 mg of PtO_2) for 4 days. The crude product (ε_{2450} 2000) was purified by chromatography on alumina, followed by crystallisation from methanol to give 3β:24-*diacetoxy*-19-*oxo-olean*-9(11)-*ene*-(XXXIII) (12 mg) as plates, m.p. 237–239°, $[\alpha]_D$ +104° (*c*, 0·9), ε_{2480} 50 (Found: C, 75·8; H, 10·0. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7 per cent). It gives a pale-yellow colour with the tetranitromethane reagent.

Vigorous oxidation of dihydrosoyasapogenol C diacetate (XXX) *with selenium dioxide.* Dihydrosoyasapogenol C diacetate (3β:24-diacetoxyolean-12-ene) was prepared as described by Meyer *et al.*[3] by catalytic reduction of soyasapogenol C diacetate; it had m.p. 188–189°, $[\alpha]_D$ +81·7° (*c*, 1·5). A solution of the dihydrodiacetate (200 mg) in benzyl acetate was oxidised with selenium dioxide as described above. The product was purified by chromatography on alumina and crystallisation from chloroform–methanol to give 3β:24-diacetoxy-12:19-dioxo-oleana-9(11):13(18)-diene (XXXI) (110 mg) as needles, m.p. 247–248°, $[\alpha]_D$ −76·7° (*c*, 1·8), λ_{max} 2760 Å (ε 13,000) (Found: C, 73·9; H, 9·0. $C_{34}H_{48}O_6$ requires C, 73·9; H, 8·75 per cent). It does not give a colour with tetranitromethane in chloroform.

3β:24-*Diacetoxy*-12:19-*dioxo-olean*-9(11)-*ene* (XXXII) A solution of the dioxodiene from dihydrosoyasapogenol C diacetate (70 mg) was reduced with zinc dust in ethanol in the usual way. The product was purified by crystallisation from chloroform–methanol to give the 3β:24-*diacetoxy*-12:19-*dioxo-olean* 9(11)-*ene* as laminae, m.p. 249–251° (dec.), $[\alpha]_D$ +120° (*c*, 1·0), λ_{max} 2450 Å (ε 12,700) (Found: C, 73·7; H, 9·3. $C_{34}H_{50}O_6$ requires C, 73·6; H, 9·1 per cent). It does not give a colour with the tetranitromethane reagent. Hydrogenolysis of 3β:24-diacetoxy-12:19-dioxo-olean-9(11)-ene by shaking its solution in acetic acid with hydrogen and platinum for 4 days gave 3β:24-diacetoxy-19-oxo-olean-9(11)-ene as plates (from methanol), m.p. and mixed m.p. 238–239°, $[\alpha]_D$ +102° (*c*, 0·8).

Acknowledgements.—We thank Sir Alexander Cross and the Cross Trust for the award of a Scholarship (to H. M. S.), the Department of Scientific and Industrial Research for a grant and Clyde Oil Extraction Ltd. for the gift of soya meal.

Tetrahedron, 1958, Vol. 4, pp. 132–134. Pergamon Press Ltd., London

THE SYNTHESIS OF PENDULETIN

S. E. Flores, J. Herrán and H. Menchaca*
Instituto de Química de la Universidad Nacional Autónoma de México,
México 20, D.F.

(*Received* 7 *March* 1958)

Abstract—A total synthesis of penduletin was achieved, conclusively proving the proposed structure for this substance.

In a recent paper[1], the structure of penduletin, a natural product isolated as its glucoside Pendulin from *Brickelia pendula* (Schrad) A. Gray, was reported to be the 4′,5-dihydroxy-3,6,7-trimethoxyflavone. There was enough evidence in favor of this formula, but it was felt necessary to carry out a total synthesis to prove it conclusively.

It was possible to synthesize penduletin (scheme 1), by following, in essence, the steps described by Goldsworthy and Robinson[2] in their first effort to synthesize tangeretin. As described under "Experimental", the end product (XIII) proved to be identical with penduletin, by the mixed melting point and the infrared absorption curves, as well as by the comparison of the 5-hydroxy-3,6,7-trimethoxy-4′-benzyloxy-flavone (XII) with the compound obtained by benzylation of penduletin. Both compounds had identical infrared spectra, the melting points were the same and the admixture did not depress it.

EXPERIMENTAL†

The sequence in the synthesis as shown in Scheme 1 was carried out, from (I) to (V), following the method of Goldsworthy and Robinson,[2] with the exception of (II) (4-nitroveratrole), which was obtained as described by Clark.[3]

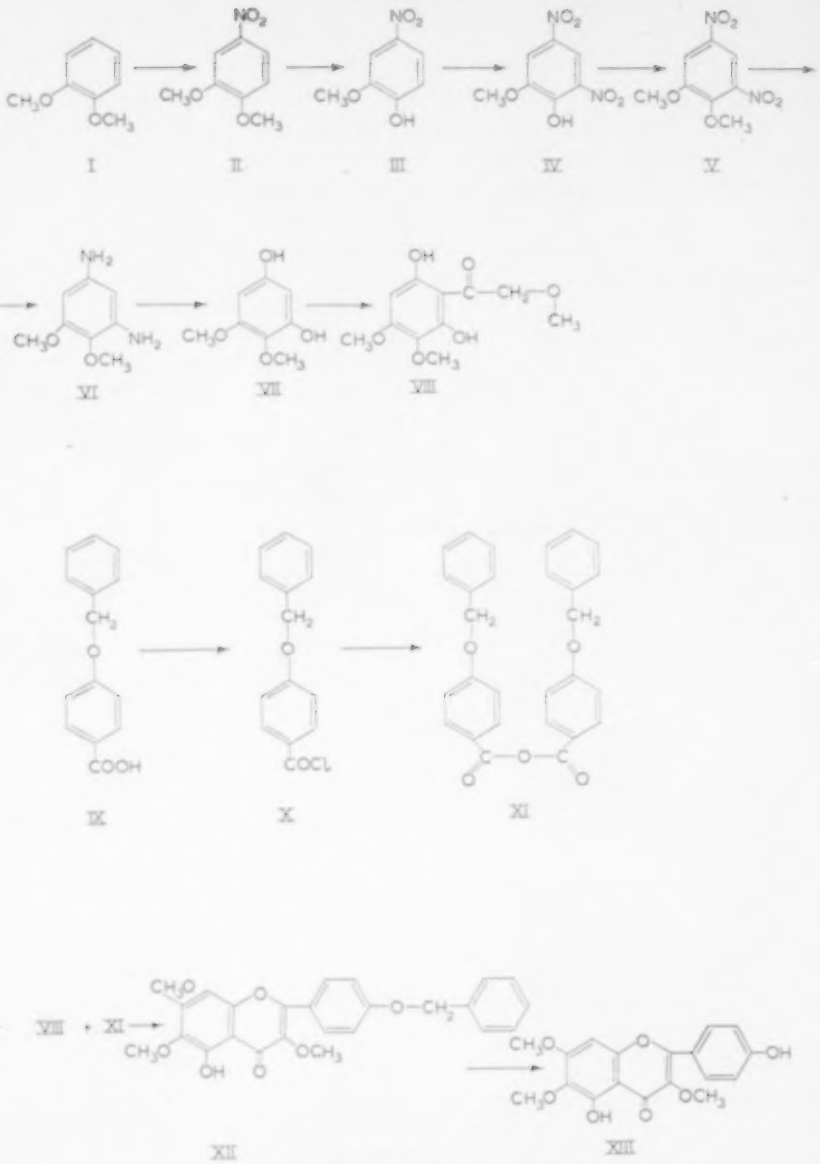
4,6-*Diaminoveratrole* (VI). 4,6-Dinitroveratrole (V) (20 g) was dissolved in ethanol (600 ml) and was hydrogenated with 1 g of 5% palladium in charcoal as catalyst. There was an absorption of 16·8 l. of hydrogen at 585 mm and 20°. After removal of the catalyst by filtration, the solution was concentrated in an atmosphere of carbon dioxide under vacuum. The white crystalline residue (12 g) showed m.p. 106–107° and gave positive tests for the *m*-diamino grouping, with nitrous acid (dark red) and with ferric chloride (purple).

4,5-*Dimethoxyresorcinol* (VII). A mixture of 10 g of 4,6-diaminoveratrole (VI), 1·8 g of crystalline stannous chloride and 500 ml of water was heated in portions in sealed tubes at 120° during 48 hr. Hydrogen sulphide was bubbled through the confined reaction products to eliminate the metallic ions as sulphides, which were filtered. The filtrate was concentrated to 75 ml (under vacuum and carbon dioxide atmosphere) and extracted with chloroform. The organic extracts were evaporated

* From the Universidad de Nuevo León, México, with a fellowship at this Institute.

† All melting points were determined with a Kofler block. The infrared spectra were determined, in Nujol, in a Perkin–Elmer model 21 double-beam spectrophotometer.

[1] S. E. Flores and J. Herrán, *Tetrahedron* **2**, 308 (1958).
[2] L. J. Goldsworthy and R. Robinson, *J. Chem. Soc.* 46 (1937).
[3] E. P. Clark, *J. Amer. Chem. Soc.* **53**, 3431 (1931).



Scheme 1

to dryness and the residue was crystallized from a very small amount of water, affording 1 g of product with m.p. 76°. The melting point, after drying under vacuum, was raised to 115–116°.

By treating the aqueous phase with more stannous chloride and repeating the hydrolysis as described, it is possible to obtain more (VII).

2,6-*Dihydroxy-ω*-3,4-*trimethoxyacetophenone* (VIII). This compound was obtained as described by Goldsworthy and Robinson[2] from (VII), and its physical constants were as described by these authors.

p-*Benzyloxybenzoic anhydride* (XI). From *p*-hydroxybenzoic acid, the benzyl ether (IX) was prepared[4] and then the corresponding acid chloride[5] (X). The anhydride XI, which was prepared by the same method,[5] showed m.p. 118–119°.

5-*Hydroxy*-3,6,7-*trimethoxy*-4′-*benzyloxyflavone* (XII). The condensation of (VIII) with (XI) was carried out as described by Goldsworthy and Robinson,[2] but the product was purified by chromatography on Magnesol as described by Ice and Wender.[6] The product (XII) showed m.p. 132–134°. By benzylation of penduletin,[1] the same compound was obtained, and a mixture of them did not show a depression of the m.p. and the infrared spectra were identical.

4′,5-*Dihydroxy*-3,6,7-*trimethoxyflavone* (*penduletin*) (XIII). The cleavage of the benzyl ether in order to obtain the desired end product was done as described by Heap and Robinson,[7] but the product was purified by chromatography on Magnesol. The product was proved to be identical with the natural penduletin[1] by the infrared spectrum and the melting point of the mixture.

[4] J. B. Cohen and H. W. Dudley, *J. Chem. Soc.* **97,** 1732 (1910).
[5] E. C. Horning, *Organic Syntheses* Coll. Vol. 3, p. 28. Wiley, New York (1955).
[6] C. H. Ice and S. H. Wender, *Analyt. Chem.* **24,** 1616 (1952).
[7] T. Heap and R. Robinson, *J. Chem. Soc.* 67 (1929).

VOL. 4 1958

Tetrahedron, 1958, Vol. 4, pp. 135–146. Pergamon Press Ltd., London

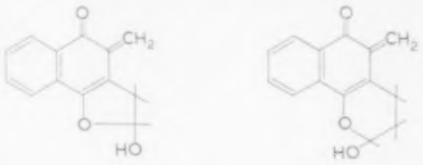
VITAMINS AND ANTIVITAMINS K: TAUTOMERISM OF DICOUMAROL

I. CHMIELEWSKA and J. CIEŚLAK
Department of Organic Chemistry, Warsaw University, Poland

(*Received* 10 *March* 1958)

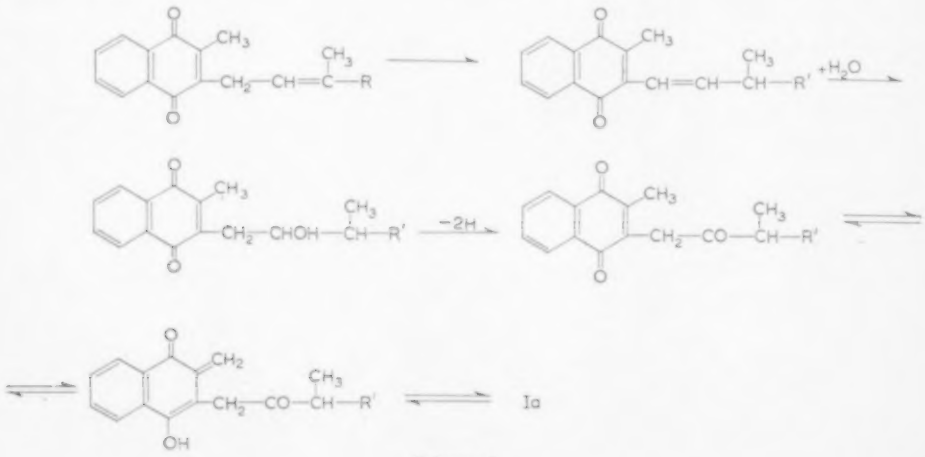
Abstract—Two isomeric dimethyl ethers of dicoumarol and derivatives substituted in the methylene group [formulae (XX) and (XXI)] were obtained. This result proves the tautomerism of dicoumarol and suggests for it the coumarin–chromone structure (XXIIa).

ACCORDING to our hypothesis, the structure necessary for vitamin-K activity is expressed by formulae (Ia) or (Ib), in which the *ortho*-quinoid group $O{=}C{-}C{=}CH_2$ acts as an active centre, while the semiketal group combines the active molecule with the protein part of the enzyme.[1]



Ia Ib

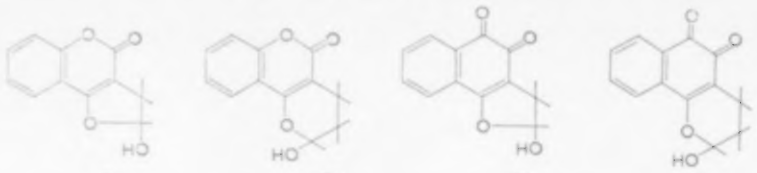
In biological conditions, the molecules represented by formula (Ia) might be formed as a result of oxidation of the phytyl or difarnesyl chain of vitamins K according to Scheme 1:



Scheme 1

For the antivitamins K we suggest the structures (IIa), (IIb), (IIIa), (IIIb), similar in shape to (Ia) or (Ib), but devoid of the active centre.[1]

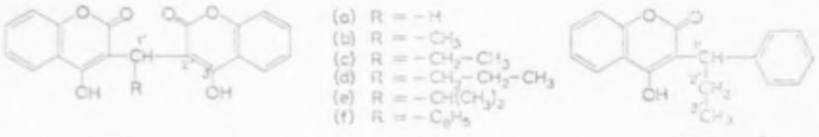
[1] I. Chmielewska, *Przem. Chem.* **29**, 740 (1950); C. Beizecki, B. Jurecka and I. Chmielewska, *Acta Physiol. Pol.* **1**, suppl., 126 (1950).



IIa IIb IIIa IIIb

The structure (IIIa), (IIIb) can be formed from the 3-substituted derivatives of 2-hydroxy-1:4-naphthoquinone. The haemorrhagic activity of several compounds of this group is known.[2,3]

The structures (IIa), (IIb) are derived from the 3-substituted-4-hydroxycoumarins. All synthetic mono-compounds belonging to this group, known before 1950, and endowed with anticoagulant activity, answered the postulates of our hypothesis, concerned the antivitamin-K activity. However, the most active compound of the group, viz., dicoumarol (IVa), as well as 3-(1′-phenyl-*n*-propyl)-4-hydroxycoumarin (V), synthesised in 1953,[4] do not fit our hypothesis. The symmetrical molecule of dicoumarol (IVa) cannot change into (IIb), and the compound (V), lacking the ketone group in position 2′, cannot form the structure (IIa).

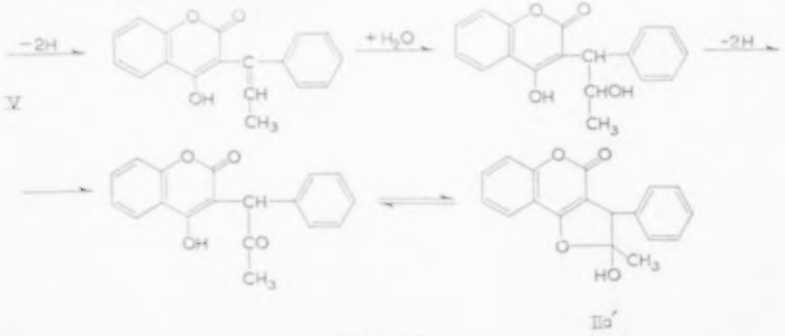


(a) R = −H
(b) R = $-CH_3$
(c) R = $-CH_2-CH_3$
(d) R = $-CH_2-CH_2-CH_3$
(e) R = $-CH(CH_3)_2$
(f) R = $-C_6H_5$

IV

Therefore our investigations on the anticoagulant activity of derivatives of 4-hydroxycoumarin were intended to disentangle the inconsistencies referred to above. Consequently, we tried (*i*) to investigate whether compound (V) may in the living organism undergo changes resulting in structure (IIa) and (*ii*) to find the tautomeric form of dicoumarol capable of assuming structure (IIb).

Compound (V) appeared likely to be transformed to the type (IIa) on biological oxidation according to Scheme 2:



V IIa′

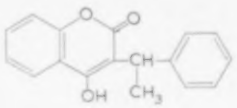
Scheme 2

[1] C. C. Smith, R. Fradkin and M. Lackey, *Proc. Soc. Exp. Biol., N.Y.* **61**, 398 (1946); C. C. Smith, *Proc. Soc. Exp., Biol. N.Y.* **64**, 45 (1947).

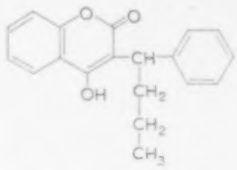
[2] I. Chmielewska and B. Jurecka, *Przem. Chem.* **29**, 5 (1950); I. Chmielewska, J. Hennig and M. Miodkowska-Iwaszkiewicz, *Przem. Chem.* **30**, 111 (1951); I. Chmielewska, H. Kowarzyk, B. Jurecka and A. Pachecka, *Prace Wrocławskiego Towarzystwa Naukowego S. B.* No. 40 (1951).

[3] R. Jürgens, *Schweiz. Med. Wschr.* **83**, 471 (1953); F. Koller and H. Jacob, *Schweiz. Med. Wschr.* **83**, 476 (1953).

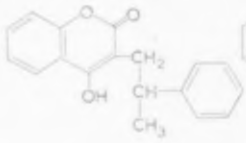
The possibility of biological oxidation in the side-chain of 3-substituted-4-hydroxycoumarins has not yet been proved. Difficulties arising in obtaining direct evidence of such a process suggested the indirect way: examination of the anticoagulant activity of the following 3-substituted-4-hydroxycoumarins (VI), (VII), (VIII) and (IX).[5]



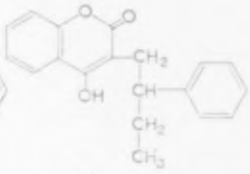
VI



VII



VIII



IX

Of the four compounds investigated only (VII) [the homologue of (V)] has the methylene group in the 2′-position and should undergo transformations according to Scheme 2. Therefore we expected its pronounced anticoagulant activity, comparable with that of dicoumarol. The remaining compounds—(VI) with a chain of two carbon atoms, (VIII) and (IX) [isomers of (V) and (VII)] with the 2′-position blocked by a phenyl residue—should not have any appreciable anticoagulant activity.

Prothrombin time in rabbits after administration of the compounds proved the activity of (VIII) and (IX) to be nil, that of (VI) negligible and that of (VII) superior to the activity of dicoumarol.[6]

The results, indicating that the 2′-methylene group is necessary for the activity of compound (V) and its analogues, seemed to confirm our assumption concerning its biological oxidation.

The structure of 3:3′-methylenebis-(4-hydroxycoumarin) (IVa) was accepted for dicoumarol,[7,8] but the tautomeric keto–enol and 2:4′-dienol structures were not impossible on theoretical grounds. However, experiments designed to prove the tautomeric forms have been unsuccessful for a long time.

The first indication of such a possibility was the discovery by Arndt *et al.* in 1951 of the coumarin–chromone tautomerism of 4-hydroxycoumarin by obtaining two isomeric methyl ethers: 4-methoxycoumarin (X) and 2-methoxychromone (XI).[9]

[5] I. Chmielewska, J. Cieślak and K. Szpalerska, *Roczn. Chem.* **30**, 813 (1956).

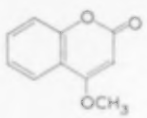
[6] Z. Latallo, J. Panasewicz, J. Cieślak and I. Chmielewska, *Bull. Acad. Pol. Sci. Cl II* **5**, 5 (1957).

[7] R. Anschütz and H. Fresenius, *Ber. Dtsch. Chem. Ges.* **36**, 465 (1903); *Liebigs Ann.* **367**, 212 (1903); *Ibid.* **379**, 336 (1916).

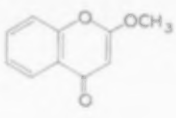
[8] R. S. Owerman, M. A. Stahmann, C. F. Huebner, W. R. Sullivan, L. Spiro, D. C. Doherty M. Ikawa, L. Graf, S. Roseman and K. P. Link, *J. Biol. Chem.* **153**, 5 (1944).

[9] F. Arndt, L. Loewe, R. Ün and E. Ayça, *Chem. Ber.* **84**, 319 (1951).

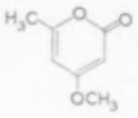
In 1952 we isolated two isomeric methyl ethers, 4-methoxy-6-methyl-2-pyrone (XII) and 2-methoxy-6-methyl-4-pyrone (XIII), and thus proved the 2:4-pyrone tautomerism of 6-methyl-2H-pyran-2:4-(3H)-dione.[10]



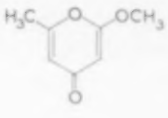
X



XI



XII



XIII

We found also a convenient method for quantitative separation of the isomeric ethers (XII) and (XIII); it consisted in adding hydrogen chloride to a cold solution of the isomers in anhydrous ether till the insoluble hydrochloride of (XIII) settled out. (XII) remained in solution and was separated after evaporation of the solvent. (XIII) was obtained from its hydrochloride by treatment with 1 equivalent of diethylamine in ether. The ratio of isomeric ethers (XII) and (XIII) was the same as that of the isometric ethers (X) and (XI) i.e., 3:1.[11]

Isomeric methyl ethers of 3:3′-*methylene bis*-(2H-*pyran*-2:4(3H)-*dione*)

The next step was the methylation of 3:3′-methylenebis-(2H-pyran-2:4-(3*H*)-dione) (XIV) with diazomethane.[12,13] This compound was used as a model in investing the possible tautomerism due to the differences in position of enolisation. The product of methylation was shown to be an equimolecular mixture of two compounds *A* and *B*. Compound *A*, m.p. 199–201°, forming no hydrochloride, was a dimethyl ether. Its properties agreed with those of (XII) and consequently structure (XVI) of 2:2′-pyrone was assigned to it. Compound *B*, m.p. 152–153°, isolated as a hydrochloride, was a monomethyl ether. Its properties corresponded to those of (XI) and (XIII), indicating the methoxy group in position 2. Since *B* could not be methylated by diazomethane, it appears reasonable to assume for it the structure (XVII) without the free enol group (Scheme 3).

Another monomethyl ether, *C*, m.p. 147–149°, isomeric with *B*, was obtained on methylation of the mono-sodium salt of (XIV) with diazomethane in methanol–ether solution. The ether *C* does not form a salt with hydrogen chloride. Further methylation furnished the dimethyl ether *A*, indicating the existence in monomethyl ether *C* of the methoxy group in the 4-position and of the free enol group (XV).

The results of methylation described above, as well as the properties of the monoethers *B* and *C*, prove the tautomerism of (XIV) and suggest that in the solid state and in ether solution the tautomeric form of a dipole structure (XVIII) predominates.

Monomethyl ether of dicoumarol

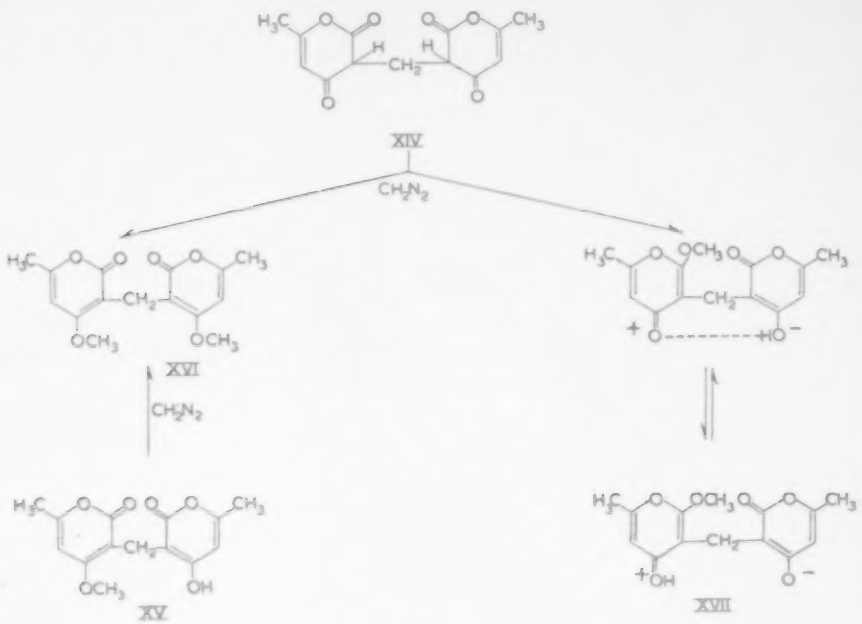
The existence of two isomeric monomethyl ethers of compound (XIV) suggested the possibility of analogous monomethyl ethers for dicoumarol. One of them,

[10] I. Chmielewska and J. Cieślak, *Przem. Chem.* **31**, 196 (1952); I. Chmielewska, J. Cieślak and T. Kraczkiewicz *Roczn. Chem.* **30**, 1009 (1956).

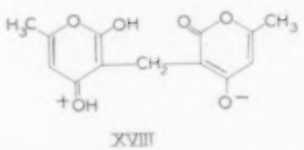
[11] J. Cieślak, *Roczn. Chem.* **26**, 483 (1952).

[12] I. Chmielewska and J. Cieślak, *Bull. Acad. Pol. Sci Cl III* **2**, 149 (1954); *Roczn. Chem.* **30**, 825 (1956).

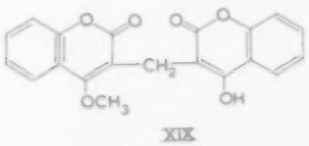
[13] J. Cieślak, Thesis, Warsaw University (1955).



Scheme 3



(XIX), m.p. 172–174°, was obtained by Link *et al.* in the reaction of epoxydicoumarol with sodium methoxide.[14] Since the methylation of dicoumarol with diazomethane furnished only a dimethyl ether, m.p. 156–158°, obtained for the first time by Link *et al.*[15] we attempted to prepare monoethers, (*a*) by demethylation of Link's dimethyl ether in methanolic hydrogen chloride or sodium hydroxide solutions; (*b*) methylation of dicoumarol with dimethyl sulphate; and (*c*) methylation of the monosodium salt of dicoumarol with diazomethane. In all cases the products obtained proved to be identical with Link's monomethyl ether. Its properties confirmed the formula (XIX), proposed by Link.



Isomeric dimethyl ethers of dicoumarol

The structure (XXa), accepted for Link's dimethyl ether of dicoumarol, agrees perfectly with many properties of this compound, except for partial demethylation in methanolic hydrogen chloride solution with formation of a monoether (XIX).

[14] C. F. Huebner, W. R. Sullivan, M. A. Stahmann and K. P. Link, *J. Amer. Chem. Soc.* **65**, 2292 (1943).
[15] H. A. Campbell, W. Roberts, W. Smith and K. P. Link, *J. Biol. Chem.* **138**, 21 (1941).

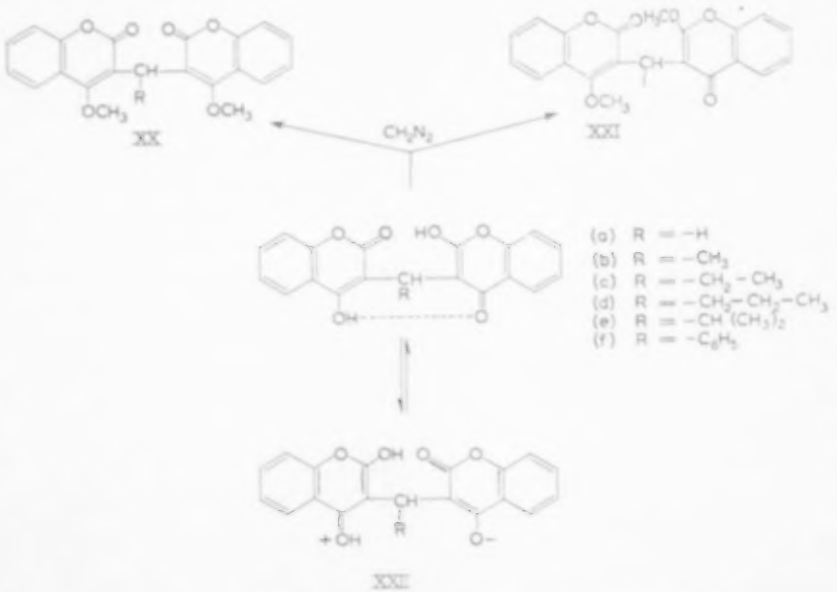
This behaviour, characteristic for 2-methyl ethers (XI), (XIII) and (XVII), was unexpected considering that Link's dimethyl ether appeared to be pure (XXa). The attempt to separate this substance into two fractions by the action of hydrogen chloride was unsuccessful. However, separation was effected through the use of perchloric acid, and the "dimethyl ether of dicoumarol" was shown to be a mixture of two isomers: D, m.p. 154–156°, which did not form a salt with perchloric acid, and E, m.p. 159–161°, perchlorate, m.p. 141–142°.

The ratio of the isomeric dimethyl ethers D and E in the methylation product of dicoumarol monomethyl ether was 5:1[16] and that in the methylation product of dicoumarol 1:1.

The properties of the dimethyl ether D agreed with the structure of 3:3′-methylene-bis-(4-methoxycoumarin) (XXa); those of E indicated the presence of the 2-methoxy-chromone ring in the molecule. It is important to note that E results on methylation of dicoumarol as well as of dicoumarol monomethyl ether (XIX). We concluded that E is 3′-(4′-methoxycoumarin)-methylene-3-(2-methoxychromone) (XXIa).

(XXIa), unlike the isomer (XXa), is not stable in methanolic hydrogen chloride solution and demethylates in the 2-position to yield the monomethyl ether (XIX).

Formation of two isomeric dimethyl ethers (XXa) and (XXIa) proves the tautomerism of dicoumarol. The 1:1 ratio of the ethers obtained by direct methylation of this compound suggests that in the solid state (the methylation with diazomethane takes place in ether suspension) the coumarin–chromone form (XXIIa) predominates.



XXII

It is interesting to note the close analogy in the structures of two "bis" compounds investigated, namely (XIV) and dicoumarol. The differences observed in the formation of its methyl ethers seems to be explained as follows. From (XIV), after introduction of the methyl group in the 2-position, the stable onium salt of the monomethyl ether

[16] I. Chmielewska and J. Cieślak, *Roczn. Chem.* **31**, 1079 (1957).

(XVII) is formed which is resistant to further methylation. Since in dicoumarol the pyrone ring is condensed with the benzene ring, the ability to form an 'onium salt after introduction of the methyl group in the 2-position is reduced. Therefore the second methyl group can be introduced to form (XXIa).

Isomeric dimethyl ethers of dicoumarol derivatives

The existence of coumarin–chromone tautomerism was then proved for several derivatives of dicoumarol substituted in the methylene bridge, namely (IVb), (IVc), (IVd), (IVe) and (IVf). The products were methylated with diazomethane and the isomeric dimethyl ethers were separated by the perchlorate method. In such a way two groups of isomeric ethers (XX) and (XXI) were obtained. Their behaviour was similar to that of the isomeric dimethyl ethers of dicoumarol.

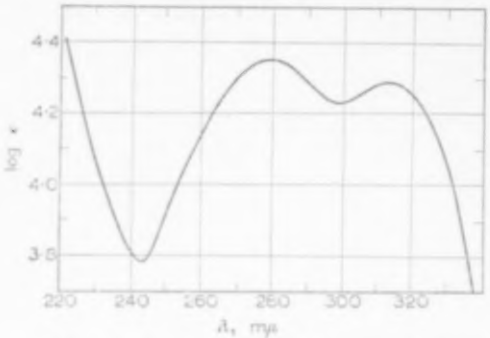


FIG. 1. Ultra-violet spectrum of compounds (XX).

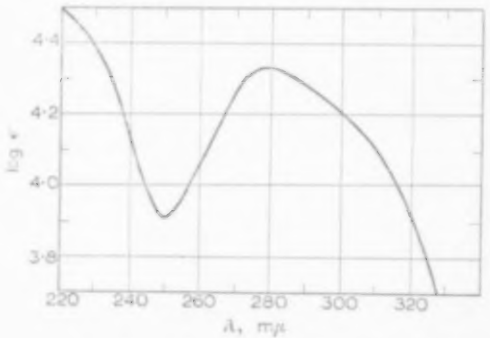


FIG. 2. Ultra-violet spectrum of compounds (XXI).

Ultra-violet spectra

All compounds within a given group have identical ultra-violet spectra, which differ from those in the other group (Figs. 1 and 2). The dimethyl ethers (XXI) show merely one maximum at 275 mμ (log ϵ 4·32) and the dimethyl ethers (XX) show two maxima, at 284 mμ (log ϵ 4·33) and at 321 mμ (log ϵ 4·28).

Infra-red spectra

In order to compare infra-red absorption of dimethyl ethers (XX) and (XXI),

we measured spectra of both 4-methoxycoumarin (X) and 2-methoxychromone (XI). The results are given in Table 1.

TABLE 1. INFRA-RED SPECTRA IN CARBON TETRACHLORIDE

4-Methoxycoumarin (μ)	5·78; 6·13; 6·40; 6·70; 6·85; 7·20; 7·55; 7·85; 8·10; 8·48; 8·75; 9·00; 9·70; 10·15; 10·75; 11·60;
2-Methoxychromone (μ)	6·05; 6·15; 6·38; 6·80; 6·90; 7·20; 7·65; 8·05; 8·48; 8·85; 9·45; 9·78; 10·45; 11·68

TABLE 2. INFRA-RED SPECTRA IN CARBON TETRACHLORIDE OF COMPOUNDS OF GENERAL FORMULAE (XX) AND (XXI)

(XXa) (μ)	(XXb) (μ)	(XXc) (μ)	(XXf) (μ)	(XXIa) (μ)	(XXIb) (μ)	(XXIc) (μ)	(XXIf) (μ)
3·38	3·40	3·40	3·40	3·40	3·40	3·40	3·40
5·80	5·80	5·80	5·82	5·80	5·85	5·83	5·82
6·13	6·18	6·18	6·18	6·15	6·18	6·18	6·18
6·35	6·38	6·40	6·40	6·36	6·40	6·40	6·43
6·70	6·70	6·70	6·72				
6·85	6·88	6·88	6·88	6·85	6·85	6·85	6·85
				7·20	7·25	7·30	7·28
7·40	7·43	7·43	7·42	7·40	7·40	7·45	7·42
7·55	7·55	7·85	7·80	7·55	7·70	7·70	7·67
7·83	7·65	8·18	8·18	7·70	8·03	7·90	8·20
8·18	7·82	8·38	8·38	8·20	8·18	8·20	8·78
8·75	8·18	8·68	8·75	8·53	8·60	8·75	9·15
9·10	8·35	8·93	9·05	8·75	9·15	9·15	9·63
9·45	8·65	9·13	9·55	8·90	9·65	9·60	10·43
10·35	9·25	9·60	10·45	9·10	10·20	10·20	
11·05	9·43	10·33		9·55	10·55	10·60	
	9·70	10·45		10·25			
	9·98	10·60		10·35			
	10·43			10·48			

In agreement with the structures assumed, 4-methoxycoumarin shows carbonyl frequency of a lactone group at 5·78 μ, and 2-methoxychromone, that of an unsaturated ketone at 6·05 μ. The same frequencies were shown, respectively, in (XII) and (XIII), as well as in the isomeric methyl ethers of other 6-substituted-2H-pyran-2: 4(3H)-diones.[12,17]

Dimethyl ethers (XX) show carbonyl frequency at 5·85 μ in agreement with the spectrum of 4-methoxycoumarin. We expected the dimethyl ether (XXI) to show carbonyl frequencies of coumarin at 5·8 μ and of chromone at 6·0 μ; unexpectedly the band at 6·0 μ did not appear in the spectra of (XXI). No explanation of this behaviour can as yet be offered.

[17] I. Chmielewska, J. Cieślak, K. Gorczyńska, B. Kontnik and K. Pistkowska, *Tetrahedron*, **4**, 36 (1958).

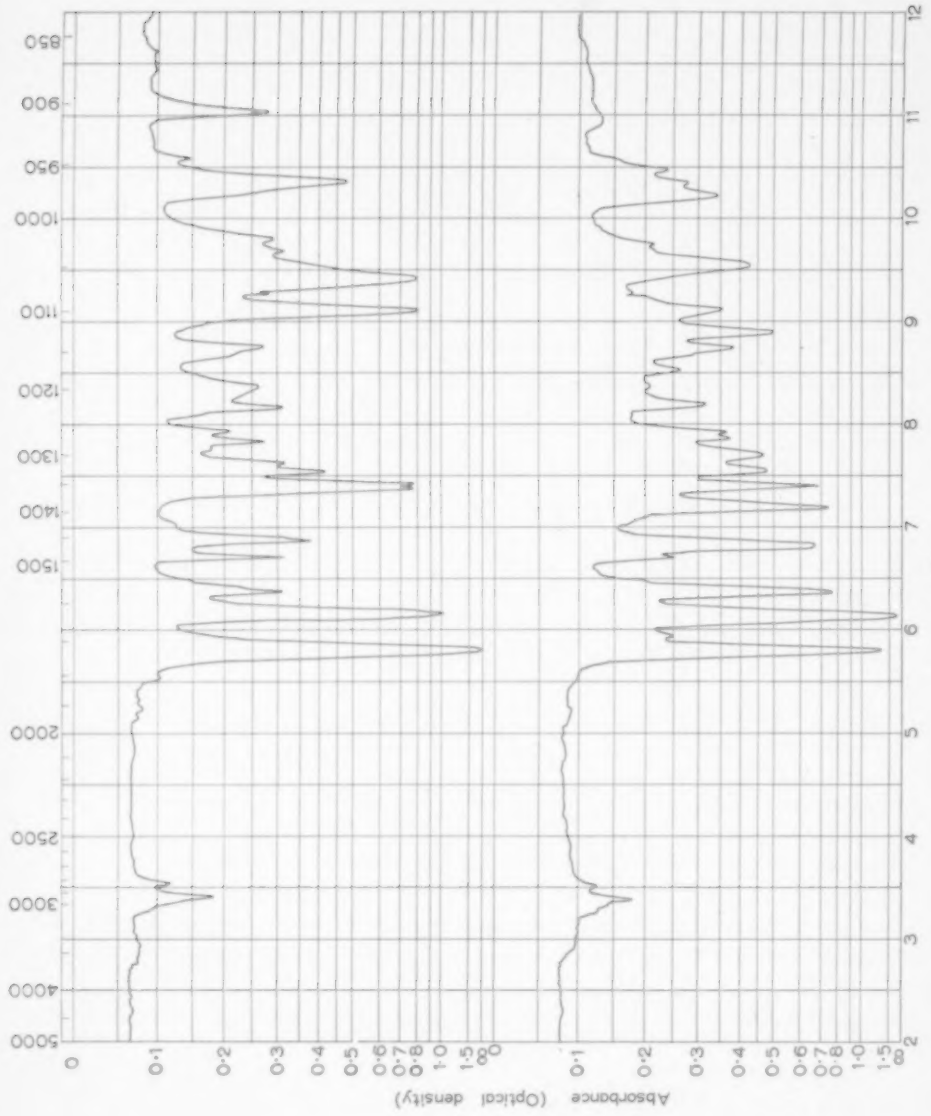


FIG. 3. Infra-red spectra in carbon tetrachloride: (1) 4:4'-dimethyl ether of dicoumarol (XXa); (2) 2,4'-dimethyl ether of dicoumarol (XXIa).

All dimethyl ethers (XX) have bands in the same position and of identical relative intensity in the region between 5·5 and 8·0 μ. Similar relationships were noted within the group of dimethyl ethers (XXI). Nevertheless, the two groups differ in absorption spectra. The relative intensity of bands in the region of 6 μ of 4:4′-diethers [5·85 μ (strong), 6·18 μ (medium)] is reversed in 2:4′-diethers [5·85 μ (medium), 6·18 μ (strong)], the band at 6·70 μ is present only in spectra of 4:4′-diethers, and the band at 7·25 μ only in those of 2:4′-diethers. Results are shown in Fig. 3 and Table 2.

Conclusion

The establishment of the tautomerism of dicoumarol appears to afford some evidence for the possibility of its transformation into the structure (Ib), necessary for the antivitamin-K activity, according to our hypothesis.

EXPERIMENTAL

Ultra-violet absorption spectra were determined in 96% ethanol with a Beckmann DU spectrophotometer. Infra-red absorption spectra were measured with a Perkin–Elmer model 21 spectrometer with a prism of sodium chloride. The compounds were examined in carbon tetrachloride solution.

The ethyl ether was dried over sodium. Some 0·05 N ethereal perchloric acid was prepared from 70% aqueous perchloric acid and dried over anhydrous magnesium sulphate. M.p. are not corrected. Compounds (IVb)–(IVf) were obtained by the method of Link *et al.*[18]

Perchlorate method. Powdered compound (IV) (0·01 mole) in ether suspension (1500 ml) was treated with diazomethane and left for 2–3 days in the cold, till a clear solution resulted. The excess of diazomethane was removed by distillation (a sample of the distillate did not react with perchloric acid) and adequate ether and 0·05 N ethereal perchloric acid (110 ml) was added in the cold. The perchlorate of (XXI) was filtered off and dried *in vacuo*.

The filtrate was washed with aqueous sodium hydrogen carbonate, then with water and dried over anhydrous magnesium sulphate. The solvent was removed and the residue (XX) was crystallised from aqueous acetone.

The perchlorate of (XXI) in methanol (50 ml) was treated with 1 equivalent of N methanolic potassium hydroxide, the potassium perchlorate was filtered off and the solvent was evaporated. Crude (XXI) was crystallised from light petroleum, boiling range 60–80°.

The yields and analytical data of compounds (XX) and (XXI) are given in Tables 3 and 4.

Demethylation of (XXIa). The dimethyl ether of dicoumarol (XXI a) (150 mg) was heated under reflux with 2% methanolic hydrogen chloride (5 ml) for 1 hr. The precipitate of epoxydicoumarol, m.p. 321–323° (30 mg), was filtered off and the filtrate was poured into water and extracted with ether. The ether extract was treated with 1% sodium hydroxide. Acidification gave dicoumarol monomethyl ether (XIX) (100 mg), m.p. 172–174°.

Dimethyl ethers (XXIb)–(XXIf) decomposed chiefly to epoxy compounds. Dimethyl ethers (XXa)–(XXf) did not change under similar conditions.

[18] W. R. Sullivan, C. F. Huebner, H. A. Stahmann and K. P. Link, *J. Amer. Chem. Soc.* **65**, 2288 (1943).

TABLE 3. YIELDS

Substrate		Perchlorate					2:4′-Diether		4:4′-Diether	
Compound taken	Amount (g)	yield (g)	m.p. (°C)	formula	OCH_3 required (%)	OCH_3 found (%)	yield of crude product (g)	m.p. of recrystallised product (°C)	yield of crude product (g)	m.p. of recrystallised product (°C)
(IVa)	3·36	2·30	141–142	$C_{21}H_{16}O_6.HClO_4$	13·35	13·10	1·80	159–161	1·80	154–156
(IVb)	3·50	2·36	144–145	$C_{22}H_{18}O_6.HClO_4$	12·96	12·75	1·86	133–135	1·90	152–153
(IVc)	3·64	2·24	150–151	$C_{23}H_{20}O_6.HClO_4$	12·59	12·38	1·78	96–98	2·11	128–129
(IVd)	3·78	2·26	163–164	$C_{24}H_{22}O_6.HClO_4$	12·24	11·97	1·80	48–51	2·24	117–119
(IVe)	3·78	1·67	160–161	$C_{24}H_{22}O_6.HClO_4$	12·24	12·02	1·67	146–148	2·70	203–204
(IVf)	4·12	1·85	161–163 (dec.)	$C_{27}H_{20}O_6.HClO_4$	11·47	11·19	1·49	200–201	2·90	182–183

TABLE 4. ANALYTICAL DATA

Compound	Formula	Required			Found		
		C (%)	H (%)	OCH_3 (%)	C (%)	H (%)	OCH_3 (%)
(XXa)	$C_{21}H_{16}O_6$	69·22	4·43	17·03	69·23	4·39	16·83
(XXIa)					69·35	4·51	17·21
(XXb)	$C_{22}H_{18}O_6$	69·83	4·79	16·40	70·00	4·59	16·25
(XXIb)					70·11	4·69	16·30
(XXc)	$C_{23}H_{20}O_6$	70·40	5·14	15·81	70·49	4·89	15·63
(XXIc)					70·50	5·04	15·59
(XXd)	$C_{24}H_{22}O_6$	70·92	5·43	15·27	71·13	5·29	15·11
(XXId)					70·70	5·59	15·08
(XXe)	$C_{24}H_{22}O_6$	70·92	5·43	15·27	71·05	5·22	15·27
(XXIe)					71·02	5·32	15·01
(XXf)	$C_{27}H_{20}O_6$	73·62	4·58	14·09	73·73	4·28	14·09
(XXIf)					73·65	4·45	13·81

Acknowledgements—We are indebted to Professor O. Achmatowicz (Institute of Organic Chemistry, Warsaw University) for helpful discussions, and to Mr. H. Frohofer (Institute of Chemistry, Zurich University) for infra-red measurements.

Tetrahedron, 1958, Vol. 4, pp. 147–156. Pergamon Press Ltd., London

A TRACER STUDY OF THE BENZOYLOXY RADICAL

C. A. BARSON* and J. C. BEVINGTON
The Chemistry Department, The University, Birmingham

(*Received* 17 *March* 1955)

Abstract—The behaviour of benzoyloxy radicals in solution at 60° has been examined by tracer methods. Benzoyl peroxide labelled with carbon-14 has been used as the source of the radicals. It has been shown that the proportion of radicals losing carbon dioxide depends upon the nature of the solvent and the concentration of peroxide and that in certain cases almost all the radicals dissociate before they can engage in other reactions. The effects of diphenylpicrylhydrazyl and thiophenol upon the reactions of the benzoyloxy radicals have been examined. From the rate of production of carbon dioxide, it is possible to measure the rate of decomposition of the peroxide. The relationship between the overall rate of decomposition and the rate of dissociation of the peroxide is discussed. New evidence is presented concerning the nature of the initiation process in the induced decomposition of the peroxide. It is concluded that the velocity constant for the dissociation of benzoyl peroxide to benzoyloxy radicals at 60° is about $1{\cdot}5 \times 10^{-6}$ sec^{-1}.

SEVERAL papers[1] have already been published concerning detailed studies of the initiation reactions when benzoyl peroxide is used as sensitiser for the polymerisation of unsaturated compounds. The work has involved the use of benzoyl peroxide labelled with carbon-14. It has been shown that tracer methods permit a direct study of the competition between the reactions:

$$C_6H_5{\cdot}CO{\cdot}O{\cdot} \longrightarrow C_6H_5{\cdot} + CO_2$$

$$CH_2{:}CH\,X + C_6H_5{\cdot}CO{\cdot}O{\cdot} \longrightarrow C_6H_5{\cdot}CO{\cdot}O{\cdot}CH\,X{\cdot}$$

This study is leading to fresh information on the factors governing the reactivities of molecules and free radicals. It has been pointed out that it is possible to determine the relative reactivities of various monomers towards the benzoyloxy radical, and also to investigate the effects of substituents upon the stability of this radical. To complete the study of benzoyloxy radicals formed by thermal dissociation of benzoyl peroxide, it is necessary to consider the behaviour of the radicals in an inert solvent; in this paper there is an account of an investigation of the decomposition of the peroxide in benzene. In addition, the effects of certain radical scavengers upon the behaviour of benzoyloxy radicals in benzene have been examined. Some observations have also been made concerning the reactions of benzoyloxy radicals in other solvents.

For the work described here, two types of labelled benzoyl peroxide were used; in the first, only the carboxyl carbon atoms were labelled, whereas in the second type the peroxide was labelled uniformly with carbon-14.

There have been many investigations concerning the nature of the products formed during the decomposition of benzoyl peroxide in solution, the latest being those of Lynch and Pausacker.[2] All the previous work has, of necessity, involved

*Present address: Bromsgrove School, Worcestershire.

[1] J. C. Bevington, *Proc. Roy. Soc.* A **239**, 420 (1957)

[2] B. M. Lynch and K. H. Pausacker, *Aust. J. Chem.* **10**, 40 (1957).

solutions of quite high concentrations and in most cases the decompositions have been allowed to proceed almost to completion. Under these conditions the decomposition is complicated by secondary reactions, in particular a radical induced decomposition. This induced reaction can be eliminated by the use of very dilute solutions in inert solvents, and the tracer techniques used in the work described here allowed the use of such solutions. Most of the work was performed with benzoyl peroxide at a concentration of 0·5 g/l. but some experiments involved solutions containing only 0·05 g/l. These concentrations are similar to those which are used when the peroxide functions as an initiator for radical chain reactions. Further, it was necessary to use only 2 ml of solution in each experiment.

Although the main object of the work was to discover the fate of the benzoyloxy radicals, the behaviour of phenyl radicals formed from them was also studied. It is hoped to present the results of this part of the work in a second paper.

EXPERIMENTAL

Labelled benzoyl peroxide was prepared from [^{14}C]benzoic acid through benzoyl chloride; it was purified by precipitation with methanol from solution in chloroform. Samples of uniformly labelled and carboxyl-labelled benzoic acid were supplied by the Radiochemical Centre, Amersham. The specific activities of the uniformly and carboxyl-labelled peroxides were, respectively, approximately 45 and 28 μc/g of carbon.

Stock solutions of the labelled peroxides were made in benzene; measured volumes were introduced into break-seal tubes and then the benzene was sublimed off at low temperatures under vacuum. A reservoir on the vacuum line contained benzene and phosphorus pentoxide; the benzene had previously been dried over sodium and fractionated. From this reservoir, benzene was distilled on the vacuum line into the reaction tubes. The solutions were degassed completely and then the tubes were sealed. The tubes were kept at 60·0° for the required time. The concentrations in the reaction mixtures were measured at 20°.

Analyses for products formed during the decomposition of the peroxide were performed by the method of isotope-dilution analysis. In the case of carbon dioxide, the break-seal tube was attached to the vacuum line and the contents were frozen in liquid air. After the seal had been broken, a known weight of inactive carbon dioxide was condensed in the tube. The active and inactive carbon dioxide were mixed by repeated thawing and freezing of the contents of the tube and by distillation of the volatile contents from the reaction tube to a second tube on the vacuum line. The carbon dioxide was then allowed to evaporate at −78°. Isotope-dilution analysis for solid products was performed by mixing the reaction mixture with appropriate carrier material in solution. The solution was evaporated to dryness at low temperature, and then a pure sample of the material under examination was isolated by repeated crystallisation. Tests with labelled contaminants showed that the following methods were suitable for purification: for benzoic acid, three crystallisations from carbon tetrachloride; for phenyl benzoate, four crystallisations from ether.

All materials were assayed by gas counting, a mixture of carbon dioxide and carbon disulphide being used.[3] Solid samples were oxidised by the method of wet combustion.

[3] J. C. Bevington, G. M. Guzman and H. W. Melville, *Proc. Roy. Soc.* A **221**, 437 (1954).

The method of calculation used in isotope-dilution analysis is well known, but mention must be made of a point in connexion with analyses for carbon dioxide produced from carboxyl-labelled peroxide. The specific activity of carbon dioxide produced during the decomposition of this type of labelled peroxide can be found only from that of the original peroxide; the specific activity, per g of carbon, for the carbon dioxide is seven times the corresponding quantity for the peroxide.

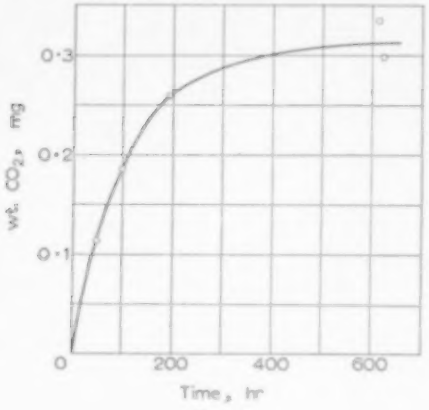


FIG. 1.

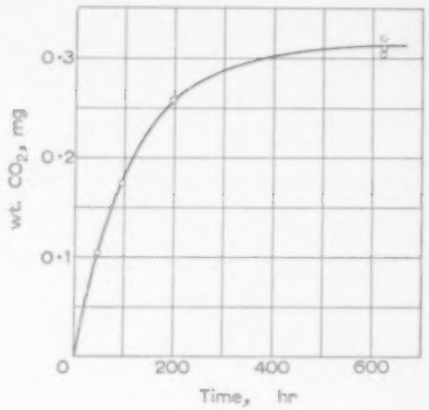


FIG. 2.

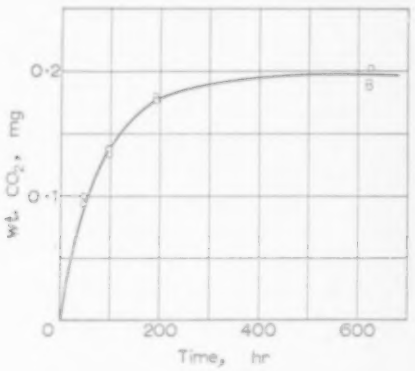


FIG. 3.

FIGS. 1, 2 and 3. The variation with time of the weight of carbon dioxide formed during the decomposition of benzoyl peroxide at 60° in benzene; starting weight of peroxide = 1 mg. Initial concentrations: Fig 1, 0·05; Fig. 2, 0·50; Fig. 3, 50 g/l.

RESULTS

Benzene as solvent

The rate of production of carbon dioxide during the decomposition of benzoyl peroxide in pure benzene at 60° was measured for three concentrations of peroxide, viz., 0·05, 0·50 and 50 g/l.; the results are presented in Figs. 1, 2 and 3.

The production of carbon dioxide and the decomposition of the peroxide follow a first-order law, since straight lines were obtained by plotting:

$$\ln \frac{w_\infty - w}{w_\infty} \quad \text{against time,}$$

where w = weight of CO_2 produced after time t,
and w_∞ = weight produced at complete decomposition of the peroxide.

A typical plot is shown in Fig. 4. The results of the experiments are summarised in Table 1.

The variation with time of the weight of benzoic acid produced during the decomposition of benzoyl peroxide in solutions of initial concentration 0·50 g/l. is shown in Fig. 5. The yields of benzoic acid under these conditions were small, only about

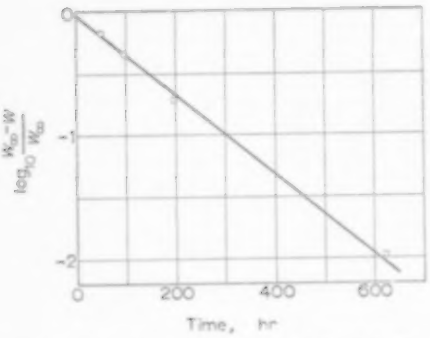


FIG. 4. A plot derived from the results shown in Fig. 2, showing that the production of carbon dioxide follows a first-order kinetic law.

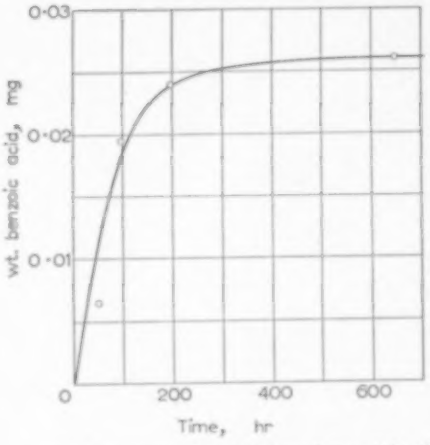


FIG. 5. The variation with time of the weight of benzoic acid formed during the decomposition of benzoyl peroxide at 60° in benzene. Initial concentration of peroxide = 0·50 g/l., initial weight of peroxide = 1 mg.

2·5 per cent of the benzoyloxy radicals being converted to the acid. The rate of decomposition of the peroxide determined from the rate of formation of benzoic acid is in fair agreement with that determined from analyses for carbon dioxide.

From similar experiments with peroxide at an initial concentration of 50 g/l., it was found that about 24 per cent of the benzoyloxy radicals were converted to the acid.

In an experiment with carboxyl-labelled benzoyl peroxide at a concentration of 0·5 g/l., 0·015 mg of phenyl benzoate were produced from 1 mg of peroxide after

TABLE 1

	Initial concentration of peroxide		
	0·05 g/l.	0·50 g/l.	50 g/l.
Weight (mg) of CO_2 from 1 mg of peroxide at complete decomposition	0·32	0·32	0·19
Percentage of benzoyloxy radicals losing CO_2	88	88	52
Velocity constant sec^{-1} for decomposition of peroxide	$2·53 \times 10^{-6}$	$2·56 \times 10^{-6}$	$4·02 \times 10^{-6}$

624 hr at 60°. Very similar yields were obtained when the concentration of the peroxide was 50 g/l.

Other solvents

When benzoyl peroxide at a concentration of 0·5 g/l. in acetic acid was decomposed at 60°, less carbon dioxide was produced than when the peroxide was decomposed in benzene under comparable conditions (see Fig. 6). The limiting yield of carbon

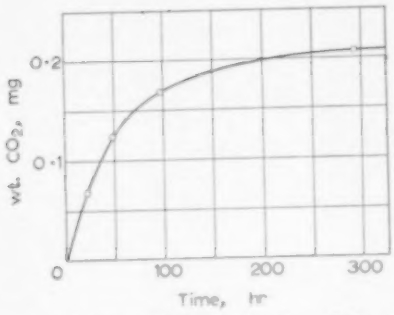


FIG. 6. The variation with time of the weight of carbon dioxide produced from benzoyl peroxide in acetic acid. Initial concentration = 0·50 g/l.

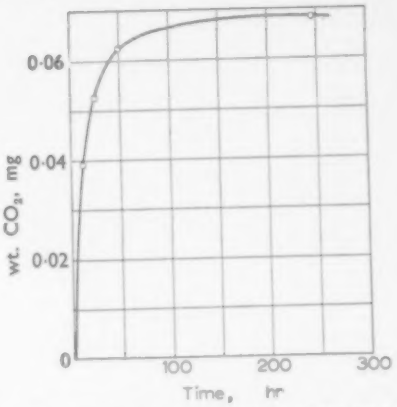


FIG. 7. The variation with time of the weight of carbon dioxide produced from benzoyl peroxide in ethanol. Initial concentration = 0·50 g/l.

dioxide was 0·214 mg from 1 mg of peroxide, corresponding to about 59 per cent. The decomposition followed a first-order law with a velocity constant of $4{\cdot}91 \times 10^{-6}$ sec^{-1}. Analyses for benzoic acid showed that 25 per cent of the benzoyloxy radicals were converted to that substance.

It was confirmed that in ethanol benzoyl peroxide decomposes rapidly. At 60° for a solution of concentration 0·5 g/l., the velocity constant was found to be $2{\cdot}15 \times 10^{-5}$ sec^{-1}; only about 22 per cent of the benzoyloxy radicals lost carbon dioxide, while about 60 per cent were converted to benzoic acid. The results for analyses for carbon dioxide are shown in Fig. 7.

With carbon tetrachloride as solvent and peroxide at a concentration of 0·5 g/l., the velocity constant at 60° was found to be $1{\cdot}39 \times 10^{-6}$ sec^{-1}. The proportion of benzoyloxy radicals losing carbon dioxide was very close to that observed when using benzene as solvent.

Effects of added substances

The yield of carbon dioxide during the decomposition of benzoyl peroxide in benzene was reduced by the presence of diphenylpicrylhydrazyl in the reaction mixture. In a series of experiments the peroxide concentration was 0·5 g/l. and the reaction mixtures were kept at 60° for 96 hr. The results are shown in Fig. 8. The concentrations of the hydrazyl were such that in all cases it was not completely consumed.

Similar experiments were performed with thiophenol in place of the hydrazyl. This substance also was very effective in reducing the yield of carbon dioxide (see Fig. 9); at the same time the yield of benzoic acid was increased (see Fig. 10).

The variations with time of the yields of benzoic acid and carbon dioxide were not studied. It is clear however that, in addition to affecting the nature of the products, thiophenol also accelerated the decomposition of the peroxide; the evidence for this is that after only 96 hr at 60° the yield of benzoic acid approached the maximum possible value.

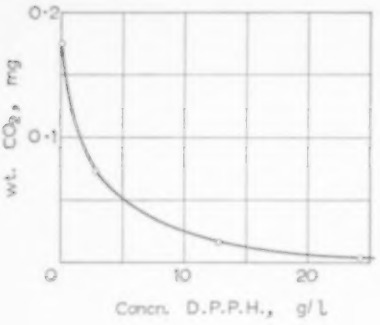
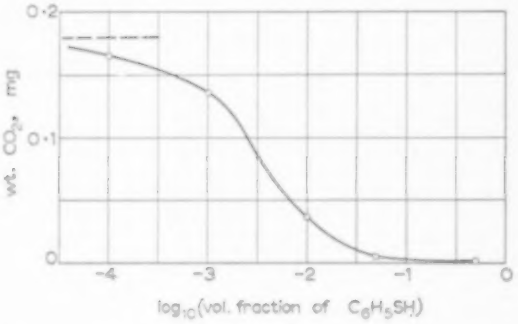


FIG. 8. The effect of diphenylpicrylhydrazyl (D.P.P.H.) upon the production of carbon dioxide during the decomposition of benzoyl peroxide in benzene at 60°. Initial concentration of peroxide = 0·50 g/l., initial weight = 1 mg, time at 60° = 96 hr.

FIG. 9. The effect of thiophenol upon the production of carbon dioxide during the decomposition of benzoyl peroxide.



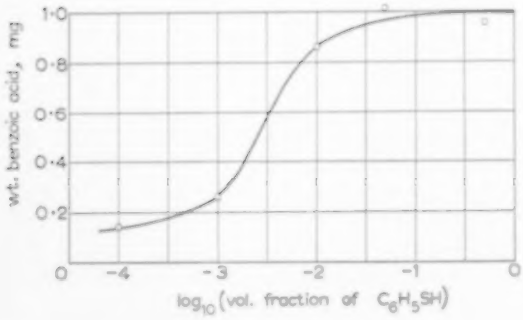


FIG. 10. The effect of thiophenol upon the production of benzoic acid during the decomposition of benzoyl peroxide.

DISCUSSION

If benzoyl peroxide is decomposed in the presence of diphenylpicrylhydrazyl or thiophenol, the yield of carbon dioxide can be reduced to zero (see Figs. 8 and 9). This shows that carbon dioxide is not produced directly during the thermal dissociation of the peroxide and that benzoyloxy radicals are the primary products of this dissociation. This is confirmed by the fact that, in the presence of sufficient thiophenol,

all the benzoyl peroxide is converted to benzoic acid (see Fig. 10). In the photodissociation of the peroxide some carbon dioxide is formed during the primary process.[4]

During the decomposition of benzoyl peroxide in dilute solutions in pure benzene at 60° about 88 per cent of the benzoyloxy radicals lose carbon dioxide before they can engage in other reactions. The proportion of the radicals decomposing in this way falls as the initial concentration of peroxide is raised (see Table 1) and in solutions containing 50 g/l. only 52 per cent of the benzoyloxy radicals dissociate. Increasing the initial concentration of peroxide also causes the yield of benzoic acid to rise and the overall rate of decomposition of the peroxide to rise.

Other workers, for example, Barnett and Vaughan,[5] also have reported that the yields of carbon dioxide during the decomposition of benzoyl peroxide depend upon the concentration of the peroxide.

The dependence of the velocity constant for the decomposition of benzoyl peroxide upon the concentration of the solution is well known and has been attributed to a radical-induced decomposition.[6] Radicals produced by dissociation of the peroxide are thought to attack other molecules of peroxide and to cause them to decompose. The importance of the induced decomposition may be reduced by decreasing the concentration of the peroxide since this will increase the chance that a radical will undergo reaction before it can encounter a molecule of undissociated peroxide. In the present work with benzene as solvent, the velocity constant was hardly affected by reducing the initial concentration from 0·5 to 0·05 g/l.; this might suggest that at these concentrations the induced decomposition is practically eliminated. At a concentration of 50 g/l. however, the induced decomposition must be of considerable importance since the velocity constant is appreciably greater than at the lower concentrations.

It appears that the induced decomposition may be started by a benzoyloxy radical abstracting a hydrogen atom from a molecule of the undissociated peroxide. In this way it would be possible to account for the decrease in the proportion of the benzoyloxy radicals losing carbon dioxide and the increase in the proportion giving benzoic acid as the initial concentration of peroxide is raised. This abstraction reaction cannot be the only cause for the decrease in the yield of carbon dioxide, since, while that yield falls from 88 to 52 per cent as the concentration of peroxide is increased from 0·5 to 50 g/l., the yield of benzoic acid rises only from about 2 to 24 per cent.

When ethanol or acetic acid is used in place of benzene as solvent, the rate of decomposition of the peroxide is significantly increased; at the same time, the yield of carbon dioxide is depressed and the yield of benzoic acid is raised. These results indicate that benzoyloxy radicals abstract hydrogen atoms quite readily from ethanol or acetic acid, and that the radicals formed from the solvent can then attack molecules of undissociated peroxide.

In considering the effects of various solvents upon the production of carbon dioxide during the decomposition of benzoyl peroxide, it is necessary to measure the yields at various stages during the reaction; measuring yields at a single time

[4] J. C. Bevington and T. D. Lewis, In preparation.
[5] B. Barnett and W. E. Vaughan, *J. Phys. Colloid Chem.* **51**, 942 (1947).
[6] K. Nozaki and P. D. Bartlett, *J. Amer. Chem. Soc.* **68**, 1686 (1946).

only may lead to erroneous results. A solvent which causes a reduction in the proportion of benzoyloxy radicals which lose carbon dioxide, may also cause an increase in the overall rate of decomposition of the peroxide; for example, the weight of carbon dioxide produced from 1 mg of peroxide after 50 hr at 60° is greater for acetic acid as solvent than for benzene as solvent, but examination of Figs. 2 and 6 shows that actually acetic acid partially suppresses the formation of carbon dioxide.

All the experiments involving thiophenol referred to 96 hr at 60°, but it has already been pointed out that this additive must have accelerated the decomposition of the peroxide. The high yields of benzoic acid in these experiments indicate that the benzoyloxy radicals abstract hydrogen atoms very readily from molecules of thiophenol leaving the radicals C_6H_5S. There is not enough information to be certain of the subsequent reactions of these radicals but some of them must attack molecules of peroxide and so induce their decomposition; none of them can combine with benzoyloxy or phenyl radicals to give stable compounds, since in some of the experiments the yield of benzoic acid approached 100 per cent.

For benzoyl peroxide at 0·5 and 50 g/l. in benzene only very small quantities of phenyl benzoate are formed during decomposition at 60°. Lynch and Pausacker,[2] using much higher concentrations of peroxide at 78°, found also that the yields of phenyl benzoate are very low. The analyses for carbon dioxide, benzoic acid and phenyl benzoate are summarised in Table 2.

TABLE 2

Solvent	Initial concn. of peroxide (g/l.)	Benzoyloxy radicals		
		losing CO_2 (per cent)	forming C_6H_5COOH (per cent)	forming $C_6H_5COOC_6H_5$ (per cent)
Benzene	0·05	88	n.d.	n.d.
Benzene	0·50	88	2·5	1
Benzene	50	52	24	1
Acetic acid	0·50	59	25	n.d.
Ethanol	0·50	22	60	n.d.
Carbon tetrachloride	0·50	88	n.d.	n.d.

n.d. = not determined

In the dilute solutions in benzene, about 90 per cent of the benzoyloxy radicals are accounted for, but in the other solutions the percentage is lower. It is concluded that in non-reactive solvents almost all the benzoyloxy radicals dissociate to give carbon dioxide unless the concentration of the peroxide is high.

Values for the velocity constant for the decomposition of benzoyl peroxide have been determined by a variety of methods;[7] the work described here gives further values found by an alternative method. It is necessary to consider whether any of the values correspond to the primary dissociation of the peroxide molecules into

[7] See, for example, G. A. Russell, *J. Amer. Chem. Soc.* **78**, 1044 (1956).

benzoyloxy radicals. The velocity constant for the decomposition of the peroxide may include a contribution from the induced decomposition, and so the lowest value observed for this velocity constant is the one most likely to correspond to the primary dissociation. High rates are observed when the concentration of peroxide in benzene is fairly high, when ethanol or acetic acid is used as solvent and when thiophenol is present in the solution; clearly under these conditions the induced decomposition is of importance. It is very significant that the rate in carbon tetrachloride is considerably less than that in benzene, even when the concentration of peroxide is low; the velocity constant found for decomposition in carbon tetrachloride and benzene, in both cases for peroxide at 0·5 g/l., are $1{\cdot}39 \times 10^{-6}$ sec^{-1} and $2{\cdot}56 \times 10^{-6}$ sec^{-1}, respectively.

One of the methods frequently employed for suppressing the induced decomposition of benzoyl peroxide is to perform the decomposition in the presence of radical scavengers; polymerisable monomers can be used for this purpose and among those which have been used are styrene,[1] dichlorostyrene[8] and methyl methacrylate.[9] It is possible that growing polymer radicals might give rise to the induced decomposition however, and this type of objection can be raised against any scavenger which reacts with radicals to give new radicals. In the case of styrene and methyl methacrylate, rates of initiation of polymerisation were measured by a tracer technique and the velocity constant for the decomposition of benzoyl peroxide at 60° was found to be $1{\cdot}5 \times 10^{-6}$ sec^{-1} (with styrene) and $1{\cdot}6 \times 10^{-6}$ sec^{-1} (with methyl methacrylate). If polystyrene and poly(methyl methacrylate) radicals are capable of inducing the decomposition of benzoyl peroxide, it would be very unlikely that they would be equally effective, and it appears that these values for the velocity constant may correspond to the primary dissociation.

The most satisfactory type of scavenger is one which reacts with radicals to give inert products incapable of further reaction with free radicals; a stabilised radical might act as a scavenger of this type. Bawn and Mellish[10] measured the rate of decomposition of benzoyl peroxide by following its reaction with the coloured radical diphenylpicrylhydrazyl. There was, however, a significant variation of velocity constant with solvent; this variation would not have been observed if the scavenger had behaved ideally. Another objection to the use of the hydrazyl is that products formed by its interaction with radicals are themselves reactive; this is shown by the fact that these products are retarders for radical polymerisations.[11]

Other workers have noticed that benzoyl peroxide decomposes rather slowly in highly halogenated solvents.[6] It is possible that these solvents favour a cage effect, so that radicals readily recombine with their original partners; it is very doubtful whether such a large difference between the rates in carbon tetrachloride and benzene could be accounted for thus, but a cage effect might be responsible for the difference between the rate observed in carbon tetrachloride and those in styrene and methyl methacrylate. The difference between the results obtained with two monomers might be accounted for by errors in the determinations of the absolute rates of polymerisation. It seems to be an inevitable conclusion that even in the very dilute solutions of

[8] C. G. Swain, W. H. Stockmayer and J. T. Clarke, *J. Amer. Chem. Soc.* **72**, 5426 (1950).
[9] J. C. Bevington, *Trans. Faraday Soc.* **53**, 997 (1957).
[10] C. E. H. Bawn and S. F. Mellish, *Trans. Faraday Soc.* **47**, 1216 (1951).
[11] J. C. Bevington, *J. Chem. Soc.* 1127 (1956).

the peroxide in benzene, there still remains a contribution from an induced decomposition; this may be initiated by the attack of phenyl radicals upon molecules of peroxide.

Acknowledgement—We thank the Dunlop Rubber Company for a maintenance grant to one of us (C. A. B.).

VOL
4
195

Tetrahedron, 1958, Vol. 4, pp. 157–168. Pergamon Press Ltd., London

A SUGGESTED STRUCTURE FOR DELSOLINE*

F. SPARATORE,† R. GREENHALGH† and LÉO MARION
Division of Pure Chemistry, National Research Council, Ottawa, Canada

(*Received* 31 *March* 1958)

Abstract—The alkaloid delsoline ($C_{25}H_{41}O_7N$) was oxidized by acid permanganate mostly to dehydro-oxodelsoline, and by neutral permanganate to anhydrohydroxydelsoline. Oxidation of the alkaloid with mercuric acetate produced anhydrohydroxy-N-de-ethyldelsoline which could be re-ethylated with ethyl iodide, thus showing the presence of an N-ethyl group in delsoline. Anhydrohydroxy-delsoline was also obtained from O-acetyldelsoline perchlorate by oxidation to an anhydronium salt followed by hydrolysis with sodium hydroxide, and this method of preparation provides evidence of its carbinolamine structure. O-Acetyloxodelsoline, obtained from acetyldelsoline, is cleaved by lead tetra-acetate to a *seco*diketone that loses the elements of methanol on recrystallization. Hence the base contains two vicinal tertiary hydroxyls, one of which is β to a methoxyl group. Dehydro-oxodelsoline is also cleaved by lead tetra-acetate and the product undergoes an internal aldol re-arrangement. These results are interpreted in the light of a structure that is tentatively suggested for delsoline.

OF the alkaloids present in *Delphinium consolida* L., delsoline was first reported by Markwood[1] and later by Cionga and Iliescu.[2] The perchlorate and hydrobromide were described by Marion and Edwards,[3] who assigned to the base the empirical formula $C_{25}H_{43}O_7N$. Delsoline has been investigated chemically, and the results now reported make it possible to advance a tentative structure for the alkaloid.

The analytical figures yielded by the base and several derivatives are in better agreement with $C_{25}H_{41}O_7N$ containing two hydrogens less than the previously assigned formula. Delsoline is a tertiary base containing four methoxyl groups and three active hydrogens that must arise from three free hydroxyls, and this accounts for all the oxygen in the molecule. One of the hydroxyls underwent acetylation quite easily and produced an amorphous derivative, which, however, formed a crystalline perchlorate. This hydroxyl, as will appear in the sequel, is secondary.

Oxidation of desoline (I) with potassium permanganate in acetone in the presence of acetic acid gave a complex mixture of neutral, basic and acidic substances. From it were isolated in small yield two bases (II) and (III), melting, respectively, at 185–187° and 218–220°, but the main fraction consisted of a neutral compound (IV), $C_{25}H_{37}O_8N$, m.p. 201°. No homogeneous product could be isolated from the acidic fraction. It must be emphasized that in all the following milder oxidation experiments no acidic material was isolated and, therefore, no primary alcoholic group appeared to be present. The neutral compound (IV) was obtained in better yield (62 per cent) when delsoline was oxidized with chromium trioxide–pyridine. Its infrared absorption spectrum contained two hydroxyl bands at 3500 and 3410 cm^{-1}, a carbonyl band at

* Issued as N.R.C. No. 4849.
† National Research Council of Canada Postdoctorate Fellow.

[1] L. N. Markwood, *J. Amer. Pharm. Ass.* **13,** 696 (1924).
[2] E. Cionga and C. Iliescu, *Ber. Dtsch. Chem. Ges.* **74,** 1031 (1941).
[3] L. Marion and O. E. Edwards, *J. Amer. Chem. Soc.* **69,** 2010 (1947).

1717 cm^{-1} indicative of a six-membered cyclic ketone and a band at 1640 cm^{-1} characteristic of a six-membered lactam carbonyl. The neutral compound (IV) is therefore a ketolactam and will be designated dehydro-oxodelsoline. It can be inferred that one of the hydroxyls in delsoline is secondary and located on a six-membered ring, while the remaining two are tertiary. Also that there is a methylene group next to the nitrogen.

That the band at 1640 cm^{-1} in the infrared spectrum of dehydro-oxodelsoline indicates a cyclic lactam and not an aliphatic amide (which is theoretically obtainable, since an N-ethyl group is present in the base, as shown below) was proved by the resistance of the compound to the action of sodium hydroxide, and to the action of hot 6 N sulphuric acid, which left about 80 per cent of the material unchanged.

The basic compound (III), m.p. 218–220°, already mentioned was obtained in much better yield when delsoline was oxidized with potassium permanganate in a solution buffered with magnesium sulphate. Its empirical formula, $C_{25}H_{39}O_7N$, differs from that of delsoline by two hydrogens. In the infrared region its spectrum contains no carbonyl nor double-bond absorption; it is similar to that of delsoline, but shows some change in the hydroxyl region, and two added sharp peaks at 998 and 897 cm^{-1}, which are probably indicative of a cyclic ether.[4] The transformation of delsoline into this new compound is accompanied by a drop of 2·2 units in pK_a (6·4 to 4·2), which suggests a change in the environment of the nitrogen. Since compound (III) does not contain more oxygen than delsoline, it cannot be a simple carbinolamine. If one of the hydroxyls in delsoline were located suitably close to react with the carbinolamine hydroxyl, an internal ether would result, and the product would contain one less hydroxyl than delsoline. Indeed, compound (III) contains one active hydrogen less than the original base. Further, compound (III) on reduction with sodium borohydride gave back delsoline, and as a simple cyclic ether would not be opened by this reagent, the compound must contain a carbinolamine ether, and will be designated anhydro-hydroxydelsoline. A similar carbinolamine ether has been observed to form in the alkaloid delcosine.[4] It should be noted that anhydrohydroxydelsoline, just like anhydro-hydroxydelcosine,[4] forms a perchlorate that is not an anhydronium salt. However, (III) was also obtained via another path that showed it clearly to be a carbinolamine ether. Oxidation of O-acetyldelsoline perchlorate with potassium permanganate in acetone, or with mercuric acetate in aqueous acetic acid, produced O-acetyldelsoline anhydronium perchlorate, and, when the aqueous solution of this salt was made basic with sodium hydroxide and heated for a short time on a steam-bath, anhydrohydroxy-delsoline (III) was formed. The course of the reactions could be represented as in Fig. 1.

The oxidation of O-acetyldelcosine with chromium trioxide–pyridine complex gave a neutral product, m.p. 148–150°, which in the infrared region showed a split lactam absorption band at 1630 and 1642 cm^{-1} and acetate bands at 1732 and 1250 $cm.^{-1}$ Unfortunately, it was not possible to obtain it sufficiently pure for analysis. After hydrolysis of the acetyl group and further oxidation with the same reagent, however, the product gave rise to dehydro–oxodelsoline (IV), thus showing that it must have consisted mostly of O-acetyloxodelsoline. The reactions described suggest that the hydroxyl involved in the internal ether formation is probably the same that is readily acetylated, and also the same that is oxidized to the ketonic group present in dehydro–oxodelsoline.

[4] R. Anet, D. W. Clayton and L. Marion, *Canad. J. Chem.* **35**, 397 (1957).

When either anhydrohydroxydelsoline or delsoline itself was oxidized with mercuric acetate in aqueous acetic acid, acetaldehyde was evolved and a compound, m.p. 185–187° was isolated in almost theoretical yield. This product was identical with compound (II) obtained in very small yield in the oxidation of the base with permanganate. It yielded analytical figures in agreement with the formula $C_{23}H_{35}O_7N$,

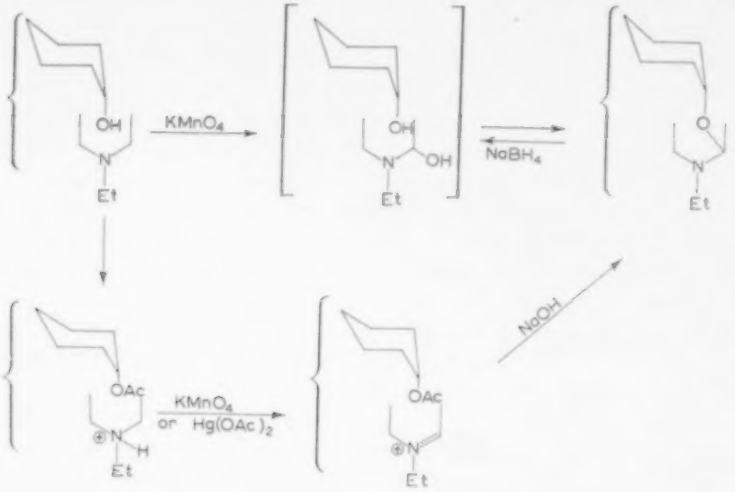


FIG. 1.

corresponding to N-de-ethylanhydrohydroxydelsoline. In fact, compound (II) on treatment with ethyl iodide in dimethylformamide was converted to anydrohydroxydelsoline (III). Consequently, delsoline in common with delcosine[4] and lycoctonine[5] is an N-ethyl base.

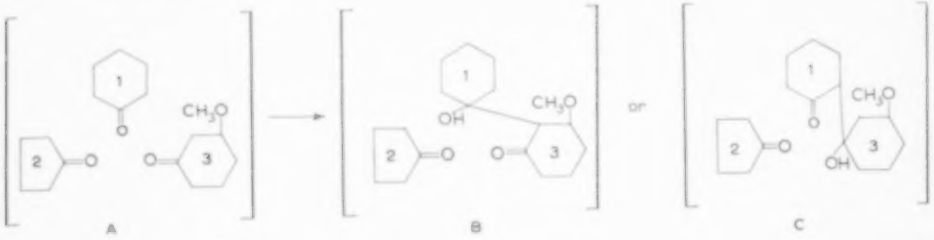
In order to establish the nature of the remaining two hydroxyls in the alkaloid, O-acetyloxodelsoline was oxidized with lead tetra-acetate. The crude reaction product, in benzene solution, was chromatographed on neutral alumina. Elution with benzene gave a small fraction that melted at 135–137°. On recrystallization from benzene–ether, the melting point jumped to 192–194°. Further elution of the chromatogram with chloroform gave a substance melting initially at 192–194°. The two products of same melting point were identical, and had an infrared spectrum showing no absorption in the OH region, but containing five characteristic sharp bands at 1740 and 1237 cm^{-1} (acetate) at 1765 cm^{-1} (*cyclo*pentane) at 1680 cm^{-1} (six membered $\alpha\beta$-unsaturated cyclic ketone)[6] and 1650 cm^{-1} (lactam carbonyl). That the cleavage product (V) (m.p. 192–194°) contained an $\alpha\beta$-unsaturated ketonic group was confirmed by the ultraviolet[7] spectrum: λ_{max} 222 mμ (log ε 3·98); λ_{max} 320 mμ (log ε 2·47); λ_{min} 272 mμ (log ε 1·88).

The analytical figures indicated the formula $C_{25}H_{35}O_8N$, showing that the reaction had involved not only the cleavage of a glycol, but also the elimination of the elements of methanol. The product (V) is therefore demethanol-O-acetyloxodelsoline *seco*-diketone. It can be concluded that delsoline contains two vicinal tertiary hydroxyls,

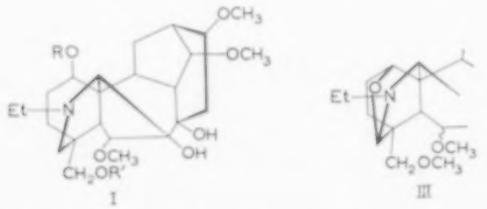
[5] O. E. Edwards and L. Marion, *Canad. J. Chem.* **32**, 1146 (1954).
[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*. Methuen, London (1954).
[7] A. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*. Edward Arnold, London (1954).

and that one of them is a substituent on a five-membered ring while the other is a substituent on a six-membered ring. Furthermore, since β-methoxyketones are known to eliminate methanol readily, it can be assumed that the tertiary hydroxyl that gives rise to the six-membered ketone is located β to a methoxyl, thus accounting for the easy elimination of methanol in the formation of (V). It seems probable that the compound melting at 135–137° first obtained from the chromatogram, might be O-acetyloxodelsoline*seco*diketone, which on recrystallization loses methanol and produces the higher-melting compound (V). This behavior parallels that of lycoctonam (oxolycoctonine) on similar oxidation.

Cleavage of the vicinal glycol system was also performed on dehydro-oxodelsoline (IV). The quantitative oxidation of (IV) with lead tetra-acetate showed a rapid uptake of 1 mole of reagent (30 min) and produced a substance (VI), $C_{25}H_{35}O_8N$, m.p. 243–245°. This product, also obtainable in much smaller yield from delsoline by oxidation with chromium trioxide in acetic acid, did not arise from a simple oxidation. Surprisingly its infrared absorption spectrum contained a hydroxyl band at 3440 cm^{-1} as well as two carbonyl bands at 1755 and 1738 cm^{-1} indicative of a five- and a six-membered cyclic ketone, and a lactam carbonyl band at 1653 cm^{-1} with a shoulder at 1640 cm^{-1}. The presence of one hydroxyl in the product (VI) was confirmed by an active-hydrogen determination (Zerewitinoff). One way to account for the presence of one hydroxyl in the product (VI) would be to assume that the expected triketone had undergone an internal aldol condensation such as has been observed with lycoctonine.[8] Such a reaction would lead to one or the other of the structures shown in the following formulae:



Since the product (VI) had not lost the elements of methanol, it appeared necessary to assume either that the carbonyl of the β-methoxyketone system was no longer present as in C, or that the α-carbon had become involved in the condensation (as in B), thus preventing the formation of a double bond. Furthermore, the only difference between O-acetyloxodelsoline and (IV), which on cleavage give rise to the two *seco*-diketones, is that the acetoxy group of the one is replaced by a carbonyl in the other.

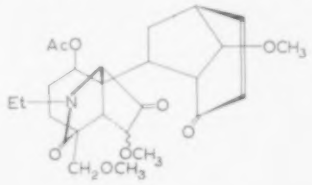


[8] O. E. Edwards and L. Marion, *Canad. J. Chem.* **32**, 195 (1954).

In the formation of (VI) it must therefore be this original carbonyl (in ring 1, formula A) that undergoes condensation with the α-methylene of ring 3 as in formula B or its neighboring methylene with the carbonyl of ring 3 as in formula C.

Since there is no evidence of unsaturation in delsoline, its structure must be hexacyclic. If the oxygenated substituents be replaced by hydrogen, the formula becomes $C_{21}H_{33}N$, just as with lycoctonine,[9] delpheline[10] and delcosine.[4] Furthermore, the chemical behavior of delsoline offers many similarities with that of lycoctonine.[8] It may therefore be assumed that the structure of delsoline is closely related to that of lycoctonine. A partial elucidation of the structure of lycoctonine was achieved initially from the chemical investigation of the base,[5,8] and an X-ray crystallographic analysis[11] made it possible to advance a total structure (I, R = CH_3, R′ = H), many features of which have since been confirmed chemically.[12] The chemistry of delsoline as established so far can be interpreted satisfactorily if it be assumed that the alkaloid possesses the same ring structure as lycoctonine, and that the substituents although partly different occupy the same positions. Structure (I, R = H, R′ = CH_3) is therefore tentatively suggested for delsoline. It must be the secondary hydroxyl that becomes involved in the formation of the carbinolamine ether in anhydrohydroxydelsoline, as shown in formula (III), and this shows clearly that the orientation of this hydroxyl has to be towards the nitrogen, and so, opposite to that of the corresponding methoxyl in lycoctonine. This orientation may account for the low pK_a of delsoline (6·4) compared with that of lycoctonine (8·8). On the other hand, the orientation of the methoxyl group on the five-membered ring adjacent to the nitrogen ring is not yet known.

The cleavage of acetyldelsoline and of dehydro-oxodelsoline with lead tetra-acetate, and the loss of methanol in the *seco*diketone obtained from the former provide evidence for the presence of vicinal tertiary hydroxyls and of a methoxyl β to one of these hydroxyls, as required by the suggested structure. Demethanol-O-acetyloxodelsoline*seco*diketone would then be represented by formula (V).



V

Attempts to obtain an anhydro derivative from dehydro-oxodelsoline (IV) through a pinacolic rearrangement, as with lycoctonam (i.e., oxolycoctonine),[4] have not so far yielded definite results. The compound (IV) was not affected when heated with acetic acid (100 ml) containing sulphuric acid (0·1 ml) at 80° or 100°, while under similar conditions oxolycoctonine gave a pinacone in 95 per cent yield.[5] Heating under reflux with acetyl chloride also failed to produce the desired change. Under more drastic conditions (treatment for a few minutes at 100° with acetic anhydride containing 5 per cent of sulphuric acid) dehydro-oxodelsoline gave a very small quantity

[9] O. E. Edwards and L. Marion, *Canad. J. Chem.* **30**, 627 (1952).
[10] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.* 2689 (1956).
[11] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).
[12] O. E. Edwards, L. Marion and D. K. R. Stewart, *Canad. J. Chem.* **34**, 1315 (1956).

of a high-melting compound (m.p. 315–320°), which had an infrared spectrum containing absorption bands indicative of a lactam carbonyl (1660 cm^{-1}) and two other carbonyl groups (1732 and 1755 cm^{-1}) that seemed to belong to two acetyl groups, since two intense bands at 1210 and 1240 cm^{-1} were also present in the spectrum. The product was not the diacetyl derivative of dehydro-oxodelsoline, since that compound was prepared and found to have different properties. Because of insufficient material no analytical figures were obtained, and any speculation as to the nature of this compound would be premature.

One attempt to correlate delsoline with lycoctonine required the inversion of the secondary hydroxyl group in the former. This was tried with dehydro-oxodelsoline by reduction with sodium borohydride, but the product of the reaction was amorphous. Since previous experience had shown that it was difficult to crystallize oxodelsoline or acetyldelsoline, the crude product of the reaction was acetylated and then oxidized with lead tetra-acetate. The *seco*diketone thus obtained crystallized well, and was identical with demethanol-acetyloxodelsoline*seco*diketone (V) prepared directly from O-acetyldelsoline, thus showing that the reduction with sodium borohydride was quite stereospecific in this case, and did not give an inversion.

Another route was explored by treating the methanesulphonyl derivative of delsoline with sodium methoxide. This reaction, however, instead of giving the expected inverted methoxyl group, hydrolyzed the mesyldelsoline and caused inversion of the hydroxyl, thus giving rise to epidelsoline. The tosylation of delsoline also produced some *epi*delsoline.

EXPERIMENTAL

The ultra-violet spectra were determined in 95% ethanol on a Beckman DU spectrometer. The infrared absorption spectra were determined on a Perkin–Elmer double-beam instrument (Model 21). In the text, the peaks are indicated by a wave number and the percentage absorption (in parentheses). Shoulders are denoted by an S after the wave number. Unless otherwise mentioned, the compounds were dispersed in Nujol mulls for the determination of the infrared spectra. All melting points were taken on a microscope hot stage and were not corrected.

Delsoline. The crude delsoline obtained from the seeds of *Delphinium consolida* L.* was heated on the steam-bath for 3 hr in a nitrogen atmosphere, with 0·5 N sodium hydroxide (water : methanol = 1 : 1) in order to hydrolyse any acetyldelsoline that could be present. The methanol was evaporated under reduced pressure and the mixture of delsoline and delcosine extracted with chloroform. The chloroform solution (dried over sodium sulphate) was evaporated to dryness under diminished pressure, and the residue was dissolved in benzene and chromatographed on Woelm alumina (activity IV, Brockmann scale). The benzene-eluted fraction was purified by repeated crystallization from 95% ethanol. The pure delsoline thus obtained melted at 213–216° (Found: C, 64·37; H, 9·01; O, 24·00; N, 2·98; OCH_3, 26·32; N—C_2H_5, 5.41; active H (Zerewitinoff), 0.73. Calc. for $C_{25}H_{41}O_7N$: C, 64·21; H, 8·84; O, 23·95; N, 3·00; $4OCH_3$, 26·56; N—C_2H_5, 6·21; 3 active H, 0·65 per cent. pK_a, 6·4 (value of pH at half titration in 50% methanol). Infrared absorption: 3442(48), 3300(36).

Monoacetyldelsoline. Delsoline (500 mg) was dissolved in dry pyridine (8 ml) and freshly distilled acetic anhydride (8 ml) was added to the solution, which was kept at

* About 5 g from 18 kg of seeds.

room temperature (25°) for 6 hr. The reaction mixture was concentrated under reduced pressure to a thick oil, which was dissolved in methanol and the solution was evaporated to dryness. The residue was dissolved in chloroform, shaken with ice-cooled 5% aqueous sodium carbonate, washed with water, dried and evaporated to dryness. The residue was dissolved in ether–pentane (1 : 1), and the solution was kept in the refrigerator for several hours and filtered to remove a small quantity of crystalline delsoline that had been deposited. The mother-liquor was evaporated to dryness, the residue was dissolved in methanol and the solution was neutralized with perchloric acid. Monacetyldelsoline perchlorate was precipitated and, after repeated crystallization from hot methanol, melted at 212–214° (Found: C, 53·16; H, 7·29. Calc. for $C_{25}H_{40}O_7N(COCH_3).HClO_4$: C, 53·15; H, 7·27 per cent). The infrared absorption spectrum of the salt contained peaks at 3430(66), 3380(60) indicative of hydroxyl groups, at 3140(64) due to an $\equiv\overset{+}{N}H$ grouping and at 1762(89), 1220(72) cm^{-1} attributable to the O-acetyl group.

Methanesulphonyldelsoline. Delsoline (300 mg) was dissolved in thoroughly dried pyridine (3 ml) and methanesulphonyl chloride was added to the solution. The mixture was left for 48 hr in the refrigerator and subsequently evaporated under reduced pressure at room temperature. The residue was dissolved in chloroform and a little ice was added to the solution, which after a few minutes was shaken with 5% aqueous sodium carbonate, dried over sodium sulphate and evaporated. The residue was washed with ether–pentane (1 : 1) and dissolved in boiling ether. The ether solution was filtered to remove an insoluble residue and concentrated until crystals began to separate. The crystalline product consisted of short thick needles (40 mg), m.p. 124°, which could not be recrystallized without some decomposition and could not be further purified (Found: C, 58·38; H, 8·52. Calc. for $C_{25}H_{40}O_7N(CH_3—SO_2—)$: C, 57·22; H, 7·94 per cent). Although the analytical figures were not very satisfactory, they seemed to indicate that the product consisted mostly of the desired substance. The infrared absorption spectrum contained the following sharp bands: 3480(60), 1165(83), 917(77), 895(72) and 875(73).

Reaction of mesyldelsoline with sodium methoxide (*epidelsoline*). Mesyldelsoline (250 mg) was added to a solution of sodium (90 mg) in absolute methanol (3 ml) and left at room temperature for 3 days The methanol was evaporated under reduced pressure, the residue was dissolved in water and the solution was extracted with chloroform. The material obtained from the chloroform was dissolved in benzene and chromatographed on Woelm alumina (activity III). The benzene-eluted material consisted of two substances, which were separated by fractional crystallization from ether. One was sparingly soluble and proved to be delsoline (probably present in the starting material), while the more soluble fraction melted at 148–154° and had an infrared absorption spectrum showing little, but very significant, difference from that of delsoline (Found: OCH_3, 26·42. Calc. for $C_{25}H_{41}O_7N$: $4OCH_3$ 26·56 per cent).

Attempted tosylation of delsoline. Toluene-*p*-sulphonyl chloride (135 mg) was dissolved in dried pyridine (2 ml) and added to a strongly cooled solution of delsoline (300 mg) in the same solvent (3 ml). The mixture was allowed to stand in the refrigerator for 60 hr. A little ice was then added and after another hour the reaction mixture was treated with aqueous sodium carbonate and extracted with chloroform. The extract was evaporated to dryness under reduced pressure and the residue was digested

with ether. An insoluble fraction was filtered out, which consisted of unchanged delsoline (170 mg). The ether-soluble material was chromatographed on Woelm neutral alumina (activity II–III). A first fraction, eluted with benzene–chloroform, consisted of delsoline, while a second fraction, eluted with chloroform containing 5% of methanol, and crystallized from ether, melted at 143–150°. The latter had an infrared absorption spectrum superimposable on that of epidelsoline.

Oxidation of delsoline with potassium permanganate [*dehydro-oxodelsoline*]. Delsoline (500 mg) was dissolved in acetone (25 ml) containing glacial acetic acid (1·5 ml) and water (1·5 ml) and oxidized by the gradual addition of finely powdered potassium permanganate. When the color of the permanganate persisted for 2 hr, the manganese dioxide was filtered off and washed twice with acetone and once with aqueous sodium carbonate. The washings and filtrate were combined, evaporated to dryness and the residue subjected to the usual separation into acid, basic and neutral fractions.

The basic fraction when chromatographed on alkaline alumina (activity V) was separated into two compounds, eluted, one with hexane–benzene, the other with benzene. When crystallized from acetone, the first compound (III) (10 mg) separated as thick needles, m.p. 218–220°. The second compound (II) crystallized from ether as fine needles, m.p. 185–187°. These two products, which have been obtained in better yields under different conditions of oxidation, are described below.

The neutral fraction when dissolved in benzene and chromatographed on alumina (activity IV) yielded 90 mg of a crystalline product, which after recrystallization from benzene–ether melted at 200–201° (Found: C, 62·46; H, 7·65; N, 3·00. Calc. for $C_{25}H_{37}O_8N$: C, 62·61; H, 7·78; N, 2·92 per cent), $[\alpha]_D^{24}$ +117·6 (*c*, 1·36 in ethanol). This product, dehydro-oxodelsoline, in solution in chloroform, showed the following bands in the infrared: 3500(44), 3410(50) due to hydroxyl groups, 1717(88) (six-membered cyclic ketone), 1640 cm^{-1} (99) (six-membered lactam carbonyl). In a Nujol mull, the bands were at 3460(68), 1717(77) and 1635(91) cm^{-1}. Further elution of the chromatogram with chloroform and methanol did not yield any crystallizable material.

The acidic fraction was very small. On treatment with diazomethane and distillation in a high vacuum, it yielded two small oily fractions, which could not be purified further.

Oxidation of delsoline with chromium trioxide. Dehydro-oxodelsoline can be obtained in much better yield when chromium trioxide is used as an oxidant. Chromium trioxide (1·2 g) was added portionwise to dry ice-cooled pyridine (12 ml) and under vigorous stirring finely powdered delsoline (1·0 g) was added to the resulting suspension. After a few minutes a black precipitate was formed, and the reaction mixture was shaken gently for 15 hr. The pyridine was evaporated under reduced pressure, and ice and 0·5 N sulphuric acid were added to the residue. Sulphur dioxide was bubbled through the solution, which was subsequently extracted with chloroform. The extract was washed with water, 4% aqueous sodium hydroxide, again with water and then evaporated to dryness. There was left a neutral residue (800 mg), which after crystallization from benzene–ether (620 mg) melted at 200–201°, either alone or in admixture with dehydro-oxodelsoline.

Dehydro-oxodelsoline is not affected by heating at 100° with either 6 N sodium hydroxide for 2 hr or 6 N sulphuric acid for 30 min. It was also recovered unchanged after heating for 1 hr at 100° with acetic acid containing 0·1% of sulphuric acid.

Treatment of dehydro-oxodelsoline with acetic anhydride containing 5% of sulphuric acid, however, yielded a very small quantity of a product, m.p. 315–320°, which could not be purified further. It had an infrared absorption spectrum that did not show clearly the presence of a hydroxyl band. It did not appear to be the expected pinacolic rearrangement product, nor was it diacetyldehydro-oxodelsoline, as shown by the preparation of that compound.

Diacetyldehydro-oxodelsoline. Dehydro-oxodelsoline (200 mg) was dissolved in acetyl chloride (10 ml) and the solution was heated under reflux for 4 hr in a nitrogen atmosphere. The acetyl chloride was evaporated under reduced pressure, ice was added to the residue, and the resulting aqueous solution was made basic with sodium carbonate and extracted with chloroform. The product (176 mg) recovered from the extract was redissolved in benzene and chromatographed on Woelm neutral alumina (activity IV). Elution with chloroform gave a substance that crystallized well from acetone–ether, m.p. 210–213° (Found: C, 62·62; H, 7·49. Calc. for $C_{29}H_{41}O_{10}N$: C, 61·79; H, 7·33 per cent). The infrared spectrum showed no absorption in the hydroxyl region, but contained bands at 1752(69), 1735(77), 1255(94) and 1240(82) cm^{-1} due to the acetyl groups, at 1720(64) cm^{-1} due to the six-membered cyclic ketone and at 1645(89) cm^{-1} attributable to the lactam carbonyl.

When this compound was hydrolyzed with 0·1 N sodium hydroxide in water and methanol, it gave back dehydro-oxodelsoline, thus confirming that it was an *OO*-diacetyl derivative.

Oxidation of delsoline with potassium permanganate under neutral conditions [*anhydrohydroxydelsoline* (III)]. Delsoline (500 mg) was dissolved in acetone (25 ml) and water (5 ml), and magnesium sulphate (3 g) was added to the solution. Under vigorous stirring, finely powdered potassium permanganate (230 mg) was added portionwise. The manganese dioxide was filtered off and washed twice with acetone–water (5 : 1). The combined filtrate and washings were evaporated under reduced pressure, the residue was dissolved in water and the solution was extracted with chloroform. The chloroform solution was evaporated to dryness and the residue, after two crystallizations from acetone, consisted of colorless hexagonal prisms (230 mg), m.p. 217–220°, either alone or in admixture with one of the minor products, compound (III), of the oxidation of delsoline with acid potassium permanganate mentioned above (Found: C, 64·33; H, 8·26; active H, 0·384. Calc. for $C_{25}H_{39}O_7N$: C, 64·49; H, 8·44; 2 active H, 0·429 per cent), $[\alpha]_D^{24}$ +57·0 (*c*, 1·27 in ethanol), pK_a 4·2 (value of pH at half titration in 50% methanol with 0·05 N hydrochloric acid). The infrared absorption spectrum contained the following characteristic bands: 3500(27), 3440(47), 3380(37), 997(85) and 895(62) cm^{-1}.

Anhydrohydroxydelsoline perchlorate. A solution of anhydrohydroxydelsoline (50 mg) in methanol (2 ml) was made just acid with 70% perchloric acid diluted with methanol. The dropwise addition of ether with stirring caused the salt to separate as hexagonal plates. After recrystallization from methanol–ether it melted at 227° (dec.). The infrared spectrum contained bands at 3460(60); 3400S(53) cm^{-1} in the hydroxyl region, and 3160(42) cm^{-1} indicative of the group $\equiv\overset{+}{N}H$, but no absorption in the 1550–1800 cm^{-1}, so that the perchlorate is not an anhydronium salt.

Reduction of anhydrohydroxydelsoline. Anhydrohydroxydelsoline (75 mg) was dissolved in 50% aqueous methanol (3 ml) and sodium borohydride (20 mg) was

added to the solution. The solution was kept at room temperature overnight, subsequently heated on the steam-bath for 1 hr and evaporated under reduced pressure to remove the methanol. The aqueous residue was extracted with chloroform, and the white powder recovered from the extract was crystallized from 95% ethanol. The crystalline product melted at 213–216°, either alone or in admixture with delsoline. A comparison of the infrared spectra confirmed the identity.

Oxidation of anhydrohydroxydelsoline with mercuric acetate [*anhydrohydroxy*-N-*de-ethyldelsoline* (II)]. To anhydrohydroxydelsoline (50 mg) dissolved in 6% aqueous acetic acid (2 ml), mercuric acetate (250 mg) was added. The solution was heated on the steam-bath for 30 min, during which acetaldehyde was evolved and was detected with Tollens's reagent. The precipitated mercurous acetate was filtered off and the filtrate was extracted with chloroform. The extract was washed with aqueous sodium bicarbonate, dried and evaporated to dryness. The residue was dissolved in ether and the solution, after filtration, evaporated to the point of incipient crystallization. Anhydrohydroxy-N-de-ethyldelsoline was thus obtained as long thin needles (37 mg), m.p. 185–187°, either alone or in admixture with compound (II) mentioned above (Found: C, 63·28; H, 8·16. Calc. for $C_{23}H_{35}O_7N$: C, 63·14; H, 8·06 per cent). Infrared absorption spectrum: 3430S(41), 3385(65), 3295(34) cm^{-1}.

Ethylation of anhydrohydroxy-N-*de-ethyldelsoline*. Anhydrohydroxy-N-de-ethyldelsoline (50 mg) was heated for 5 hr on the steam-bath with ethyl iodide (600 mg), dimethylformamide (300 mg) and sodium carbonate (20 mg). The product, crystallized from acetone–ether, melted at 217–219°, either alone or in admixture with anhydrohydroxydelsoline. The identity was confirmed by comparison of the infrared spectra.

Oxidation of delsoline with mercuric acetate. Delsoline (300 mg) was dissolved in 6% aqueous acetic acid (12 ml), mercuric acetate (1500 mg) was added and the solution was heated on the steam-bath for 60 min. The precipitated mercurous acetate was filtered off and washed with 6% aqueous acetic acid, and the combined filtrate and washings were extracted with chloroform. The extract was washed with aqueous sodium bicarbonate and with water, dried and evaporated to dryness. There was left a residue, which after crystallization from ether (yield 120 mg) melted at 184–186°, alone or in admixture with anhydrohydroxy-N-de-ethyldelsoline (II) described above.

Oxidation of acetyldelsoline perchlorate with potassium permanganate. To a solution of acetyldelsoline perchlorate (305 mg) in acetone (25 ml) and water (5 ml), finely powdered potassium permanganate (57 mg) was added. The permanganate was reduced rapidly, and the manganese dioxide was filtered off and washed with acetone–water. The filtrate was evaporated to dryness under reduced pressure. The solid residue left was washed several times with boiling ether. The combined ether solutions yielded a quantity of acetyldelsoline. The residue (116 mg), which was insoluble in ether, consisted of acetyldelsoline anhydronium perchlorate and potassium perchlorate. It was dissolved in hot absolute ethanol in which potassium perchlorate was less soluble than the anhydronium salt. After many separations and crystallizations from absolute ethanol, the anhydronium salt was obtained as thin needles, m.p. 253–255° (dec.). The analysis showed that the sample still contained a little potassium perchlorate. The infrared spectrum of acetyldelsoline anhydronium perchlorate contained the following absorption bands: 3440(68), 3360(58) (hydroxyl); 1760(71), 1748(87), 1230(91) (acetate); 1690(33) cm^{-1} due to $-C=\overset{+}{N}\!\!<$.

Oxidation of acetyldelsoline perchlorate with mercuric acetate. Acetyldelsoline perchlorate (305 mg) was dissolved in 6% aqueous acetic acid (12 ml) and acetone (6 ml). Mercuric acetate (1·0 g) was added and the solution was heated for a short time on a steam-bath. The precipitated mercurous acetate was filtered off and the remaining mercury salt was removed with hydrogen sulphide. The filtered solution was evaporated to dryness under reduced pressure and the residue (acetyldelsoline anhydronium perchlorate) was crystallized from ethanol as before.

Reaction of acetyldelsoline anhydronium perchlorate with sodium hydroxide. Acetyldelsoline anhydronium perchlorate (20 mg) was dissolved in water (4 ml), 6 N sodium hydroxide (0·5 ml) was added and the solution was heated for 15 min on the steam-bath. The cooled solution was extracted with chloroform and the extract was evaporated to dryness. There was left a residue which crystallized from acetone (yield 12 mg), m.p. 216–219° either alone or in admixture with anhydrohydroxydelsoline. The identity was confirmed by the infrared absorption spectra which were superimposable.

Oxidation of acetyldelsoline. Acetyldelsoline perchlorate (610 mg) was suspended in ice-cooled water (10 ml) and chloroform. The suspension was stirred vigorously while cooled externally and N sodium hydroxide (12 ml) was added. After a few minutes the chloroform solution was separated and the aqueous layer was extracted several times with chloroform. The combined chloroform solution was dried and evaporated to dryness under diminished pressure. The residue, dissolved in pyridine (3 ml), was added to a suspension of chromium trioxide (400 mg) in pyridine (9 ml). After it had been kept gently shaking overnight, the reaction mixture was worked up in the same way as described for the oxidation of delsoline. The chloroform extract was washed with water, with ice-cooled sodium carbonate solution, again with water and then dried over sodium sulphate. The residue obtained after the evaporation of the chloroform extract was dissolved in a little benzene, and pentane was added. After 2 days in the cold a few crystals had been deposited, m.p. 148–150°. The residue left after evaporation of the mother-liquor was a colorless glass. The infrared spectra of the crystals and of the glass did not show any important difference. The main absorption bands were: 3460(55), 3420(54) due to hydroxyls, 1732(92), 1250(95) due to an acetate group and 1640(90), 1630(90) cm^{-1} indicative of a lactam carbonyl.

Oxidation of acetyloxodelsoline [*demethanol-acetyloxodelsoline*seco*diketone* (V)]. Acetyldelsoline (200 mg) was dissolved in 20 ml of an acetic acid solution of lead tetra-acetate (2 g in 75 ml) and left to stand for 90 min. A saturated solution of sodium metasulphite was added until no reaction was obtained on a starch–iodide paper. A small quantity of Cellite was added and the solution was centrifuged. The clear acid centrifugate was evaporated to dryness under reduced pressure, the residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate. Evaporation of the dried chloroform solution left an oil, which was dissolved in benzene and chromatographed on Woelm neutral alumina (activity IV). The material eluted with benzene was obtained as a glassy substance that crystallized when ether and pentane were added as fine needles, m.p. 135–137°. On recrystallization from benzene–ether the melting point jumped to 192–194°, presumably showing a change in the nature of the compound. Further elution of the chromatogram with chloroform yielded a second fraction that crystallized on contact with ether, m.p. 187–193°, and after recrystallization from benzene–ether, at 192–194°. It was identical with the

above-mentioned compound (Found: C, 63·48; H, 6·98. Calc. for $C_{26}H_{35}O_8N$: C, 63·79; H, 7·21 per cent). Ultraviolet absorption spectrum: λ_{max} 222 mμ, (log ε 3·98), λ_{min} 277 mμ (log ε 1·88), λ_{max} 319 mμ (log ε 2·47). The infrared spectrum contained bands at 1765(73), five-membered cyclic ketone; 1740(88), 1237(93) (acetate), 1680(75), $\alpha\beta$-unsaturated six-membered ketone, 1650(93) cm^{-1} (lactam).

Hydrolysis and oxidation of acetyloxodelsoline. Acetyloxodelsoline (100 mg) was heated on a steam-bath with N sodium hydroxide for 30 min. The cooled solution was extracted with chloroform and the extract on evaporation yielded oxodelsoline as a colorless glass. The glass was dissolved in dry pyridine (1 ml) and added to a suspension of chromium trioxide (100 mg) in pyridine (1 ml). After 15 hr the reaction mixture was worked up as described before. The residue obtained after evaporation of the chloroform extract was crystallized from benzene–ether, m.p. 199–201°, either alone or in admixture with dehydro-oxodelsoline.

Reduction of dehydro-oxodelsoline with sodium borohydride. To a solution of dehydro-oxodelsoline (230 mg) in 1 : 1 aqueous methanol (8 ml), sodium borohydride (230 mg) was added and the solution was allowed to stand overnight. Methanol was distilled off under reduced pressure, water was added and the solution was extracted with chloroform. Evaporation of the extract left a clear glassy material (180 mg), which could not be crystallized.

The glassy material (180 mg) thus obtained was treated with acetic anhydride (3 ml) and pyridine (3 ml) at room temperature for 6 hr. The colorless amorphous product (isolated as previously described) was dissolved in 10 ml of an acetic acid solution of lead tetra-acetate (2 g in 75 ml of acetic acid). After 90 min the reaction mixture was worked up as already described for the similar oxidation of acetyloxodelsoline, and the same demethanol-acetyloxodelsoline*seco*diketone, m.p. 192–194°, was obtained. Hence the reduction with sodium borohydride must have heen stereospecific.

Oxidation of dehydro-oxodelsoline with lead tetra-acetate. The keto-lactam (79 mg) was dissolved in acetic acid (15 ml) containing lead tetra-acetate (2 g per 75 ml of acid) and left to stand for 1 hr. Titration at the end of 1 hr determined that 1·16 moles had been taken up. A saturated solution of sodium metabisulphite was added until no reaction was obtained with starch–iodide paper. Some Cellite was added and the solution was centrifuged. The clear acid solution was then evaporated to dryness under reduced pressure, the residue was dissolved in aqueous sodium bicarbonate and the solution was extracted with chloroform. The oil recovered from the chloroform extract was chromatographed on Woelm neutral alumina (activity IV) and eluted with chloroform. A fraction (60 mg) was thus obtained which crystallized from methanol–ether (yield 75 per cent), m.p. 243–245° (Found: C, 62·49; H, 6·95. Calc. for $C_{25}H_{35}O_8N$: C, 62·57; H, 7·37 per cent). Infrared absorption: 3440(61), 1755(85), 1738(82), 1653(90), 1640S(66) cm^{-1}.

Acknowledgement—We gratefully acknowledge our indebtedness to Dr. R. Norman Jones and Mr. R. Lauzon of these laboratories for the determination of the infrared absorption spectra.

VOL. 4 195

Tetrahedron, 1958, Vol. 4, pp. 169–177. Pergamon Press Ltd., London

STUDIES IN PEROXIDASE ACTION—XII*

TRANSIODINATION AND RELATED PROCESSES

B. C. SAUNDERS and B. P. STARK
University Chemical Laboratory, Lensfield Rd., Cambridge

(*Received* 15 *April* 1958)

Abstract—The investigations reported here suggest that the enzyme peroxidase (which is known to exist in the mammalian thyroid gland[1]) may be concerned in a fundamental way with the transport of iodine. Further studies with systems containing both the enzyme and iodine suggest possible connections between peroxidase action, iodine metabolism and natural phosphorylation processes and the formation of disulphide links.

ACCORDING to a recent suggestion by Ljunggren,[2] a peroxidase may be involved in the formation of thyroxine from di-iodotyrosine. Daniels and Saunders[3] showed that the peroxidase system at pH 4·5 converted *p*-chloroaniline into 2-amino-5-*p*-chloroanilinobenzoquinone di-*p*-chloroanil and tetra-*p*-chloroazophenine. This took place with the facile removal of the relatively stable chlorine atom from *p*-chloroaniline as chloride ion. It was furthermore shown that the chloride ion was produced quantitatively. *p*-Iodoaniline behaved somewhat similarly in giving the corresponding crystalline organo-iodine compounds; here, however, the iodine, which was first eliminated as I^-, was then oxidised completely to I_2 (an oxidation known to be accelerated by peroxidase). This immediately iodinated some unchanged iodoaniline to give 2:4-di-iodoaniline. Thus we had an example of de-iodination followed by re-iodination. The reaction has now been extended so that a compound other than the original substrate becomes the "iodine acceptor." Thus the peroxidase system is able to effect a process that we may call *transiodination*.

We have accordingly investigated a number of reactions involving this intermolecular transfer of iodine under the influence of the peroxidase system; particular attention has been paid to reactions with compounds similar to those present in the thyroid gland. Our results are shown in Table 1.

The reactions were carried out at room temperature by the intermittent addition of peroxidase and hydrogen peroxide to mixtures of iodine donor and acceptor in weakly acid buffer solutions. Under these conditions the use of phenolic ethers as iodine acceptors gave products containing only traces of iodine. These results would seem to be in agreement with those of Gemmill,[4] who observed that iodination of phenolic amino acids in aqueous solution led to substitution at positions *ortho* to phenolic hydroxyl groups but not at positions *ortho* to ether linkages. Higher yields of

* Paper XI, G. M. K. Hughes and B. C. Saunders *J. Chem. Soc.* 3814 (1956).

[1] E. De Robertis and R. Grasso, *Endocrinology* **38**, 137 (1946).

[2] J. -G. Ljunggren, *Acta Chem. Scand.* **11**, 1072 (1957).

[3] D. G. H. Daniels and B. C. Saunders, *J. Chem. Soc.* 822 (1953); B. C. Saunders, *Peroxidase Action and Use in Organic Synthesis.* Royal Institute of Chemistry Lectures, Monographs and Reports No. 1, London (1957).

[4] C. L. Gemmill, *Arch. Biochem. Biophys.* **63**, 177 (1956).

iodinated acceptors could be obtained by reaction in multi-phase systems, when, for instance, phenol gave a good yield of tri-iodophenol.

TABLE 1. RESULTS OF TRANSIODINATION REACTIONS

Iodine donor	Iodine acceptor	Transiodinated product
p-Iodoaniline	Pyrrole	Tetraiodopyrrole
4-Iodo-2:6-dimethylphenol	Indole	3-Iodoindole
4-Iodo-2:6-dimethylaniline	Phenol	Tri-iodophenol
4-Iodo-2:6-dimethylaniline	*p*-Hydroxyphenylacetic acid	3:5-Di-iodo-4-hydroxy-phenylacetic acid
4-Iodo-2:6-dimethylphenol	Tyrosine	Mono- and di-iodotyrosines
Di-iodotyrosine	Thyronine	3′-Iodothyronine
Di-iodotyrosine	3:5-Di-iodothyronine	Thyroxine
3-Iodotyrosine	3-Iodotyrosine	3:5-Di-iodotyrosine

We next decided to investigate other reactions in which peroxidase systems in the presence of iodine might be utilised. McCombie *et al.*[5] obtained quantitative yields of phosphoroiodidates by the action of iodine on trialkyl phosphites:

$$(RO)_3P + I_2 = (RO)_2POI + RI$$

The same workers observed, however, that, when dialkyl hydrogen phosphites were used in place of the trialkyl phosphites, negligible reaction occurred. They suggested that the hydrogen iodide first formed interfered with the formation of phosphoroiodidate, perhaps by virtue of a reversible reaction:

$$(RO)_2POH + I_2 \rightleftharpoons (RO)_2POI + HI$$

Gerrard and Jeacocke[6] suggested that dealkylation of the hydrogen phosphite by the hydrogen iodide formed as above prevented the formation of phosphoroiodidate. It seemed then that, if the reaction between iodine (or an iodine donor) and a dialkyl phosphite could be carried out in the presence of peroxidase, then a high yield of the phosphoroiodidate should result. This has indeed been found to be the case.

Since phosphoroiodidates react with amines to give dialkyl phosphoramidates and iodide,[5] it was thought worth while to investigate the formation of phosphorus–nitrogen bonds in the presence of the enzyme. Such a system was found to give good yields of phosphoramidate.

It is known that the controlled hydrolysis of phosphorochloridates yields tetraalkyl pyrophosphates and halide.[7] Here again it seemed that the enzyme system might be used in the formation of P–O–P links. Preliminary experiments showed that careful hydrolysis of diethyl phosphoroiodidate led to the formation of tetraethyl pyrophosphate (TEPP). Separate experiments showed that addition of iodine to aqueous solutions of tri*cyclo*hexyl phosphite gave di*cyclo*hexyl hydrogen phosphate, formed by hydrolysis of the phosphoroiodidate. On the other hand, a small yield of TEPP could be obtained by careful addition of peroxidase and peroxide to solutions containing

[5] H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.* 921 (1945).
[6] W. Gerrard and G. J. Jeacocke, *J. Chem. Soc.* 3647 (1954).
[7] A. D. F. Toy, *J. Amer. Chem. Soc.* **70**, 3882 (1948).

triethyl phosphite and iodide in the presence of a limited amount of water. In this latter reaction, iodide was continually oxidised by the enzyme to iodine, which could re-enter the cycle:

$$(RO)_3P + I_2 = (RO)_2POI + RI$$
$$(RO)_2POI + H_2O = (RO)_2P(O)OH + HI$$
$$(RO)_2POI + (RO)_2P(O)OH = (RO)_2P(O)OP(O)(OR)_2 + HI$$
$$2HI + H_2O_2 \xrightarrow{\text{peroxidase}} I_2$$

Phosphorylation reactions involving dialkyl phosphites have also been considered. As explained above, the removal of hydrogen iodide is essential for the complete formation of phosphoroiodidate. In our work, hydrogen iodide has been removed either by oxidation with the peroxidase system, or by precipitation as a tertiary base hydriodide. In the reaction scheme given below, a cyclic formation and oxidation of iodide continually occurs; thus the peroxidase system is able to bring about the formation of phosphates, pyrophosphates and phosphoramidates in the presence of only catalytic amounts of iodine:

$$(RO)_2POH + I_2 = (RO)_2POI + HI$$
$$(RO)_2POI + H_2O = (RO)_2P(O)OH + HI$$
$$(RO)_2POI + (RO)_2P(O)OH = (RO)_2P(O)OP(O)(OR)_2 + HI$$
$$(RO)_2POI + R'NH_2 = (RO)_2P(O)NHR' + HI$$
$$4HI + 2H_2O_2 \xrightarrow{\text{peroxidase}} 2I_2$$

Some typical results may be summarised thus. Reaction of peroxidase, peroxide and iodine with di*cyclo*hexyl phosphite in the presence of much water gave di*cyclo*hexyl hydrogen phosphate; diethyl phosphite in the presence of a limited amount of water gave TEPP in small yield. Higher yields of TEPP could be obtained by precipitation of hydrogen iodide with pyridine, in the presence of a limited amount of water; moreover, addition of aniline to the phosphoroiodidate thus formed gave diethyl N-phenylphosphoramidate, while gradual addition of iodine (again from peroxidase oxidation) to mixtures of benzylamine and di*tert*.-butyl phosphite gave di*tert*.-butyl N-benzylphosphoramidate.

Brief study has also been made of the formation of disulphide linkages from sulphydryl groups by the action of peroxidase and iodine. Here again, hydrogen iodide is formed, oxidised and returned to an earlier part of the cycle as iodine:

$$2RSH + I_2 = R\text{–}S\text{–}S\text{–}R + 2HI$$
$$2HI + H_2O_2 \xrightarrow{\text{peroxidase}} I_2$$

Thus cysteine was readily converted to cystine by the action of peroxidase and hydrogen peroxide, in the presence of di-iodotyrosine as iodine donor. This type of oxidation may be of interest in connexion with the recent description by Mills[8] of a "glutathione peroxidase" and his suggestion that this enzyme may have the effect of protecting haemoglobin from oxidative breakdown.

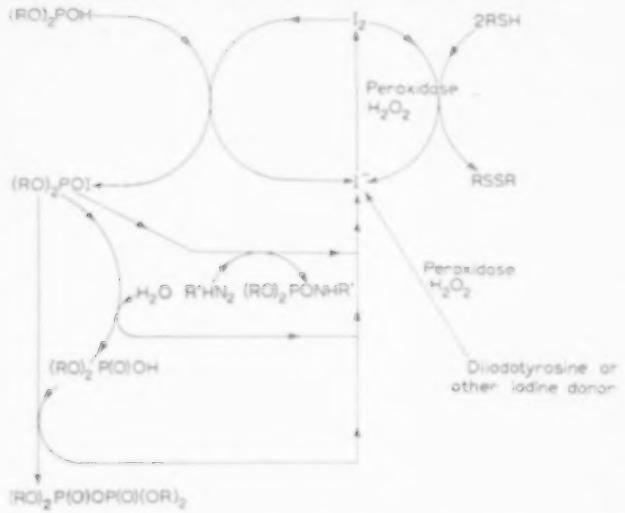
It is now convenient to summarise the action of iodine in phosphorylation and oxidation processes. It is known that some 8 μg of iodine are present in 100 ml of

[8] G. C. Mills, *J. Biol. Chem.* **229**, 189 (1957).

systemic blood, and the present work may serve to indicate possible functions of this circulating iodine. Furthermore, we have emphasised the triple function of peroxidase in this connexion: (*a*) the release of iodine from an iodine donor, (*b*) the actual transfer of iodine—"transiodination," (*c*) the oxidation of iodide to iodine, hence the circulation of iodine is ensured.

All these processes may conveniently be represented by the scheme shown in Table 2.

TABLE 2. PEROXIDASE OXIDATION–PHOSPHORYLATION CYCLES



In general, in the transiodinations described above the yields were low, but it must be remembered that these *in vitro* reactions have been carried out entirely in aqueous media, whereas the physical many phase structure of the animal cell may well permit a more efficient iodine transport process.

It may be argued that some of the substances used in the phosphorylation reactions are somewhat artificial, but nevertheless they serve to represent certain new general principles, which may be capable of extension to materials having a more biological significance.

EXPERIMENTAL

Peroxidase solution. Two enzyme preparations were used; one was a concentrated solution (P.N. ca. 500) of horse-radish peroxidase, kindly supplied by Professor Keilin, and the other was a less active enzyme preparation (P.N. ca. 10) obtained from turnips.[9]

Transiodinations

(a) *From* p-*iodoaniline to pyrrole.* Turnip peroxidase and hydrogen peroxide (20 volume) were added at intervals to *p*-iodoaniline[10] (21·9 g, 0·1 mole) and pyrrole (3·35 g, 0·05 mole) in acetate buffer solution (2900 ml, 0·1 M, pH 4·7), a total of 150 ml

[9] F. G. Mann and B. C. Saunders, *Practical Organic Chemistry* (3rd. Ed.) p. 420. Longmans, Green, London (1952).

[10] R. Q. Brewster, *Organic Syntheses* Vol. XI, p. 62. Wiley, New York (1931).

of enzyme solution and 70 ml of peroxide being added. The mixture was filtered and the precipitate was suspended in dilute hydrochloric acid (500 ml, 3 N) and extracted with ether (4 × 250 ml). The ether-soluble material was dried and washed with chloroform (50 ml at 0°) and extracted with benzene (150 ml). The benzene-soluble material was extracted with ethanol (150 ml) and the dissolved material was chromatographed on alumina, when crude tetraiodopyrrole was obtained. Repeated recrystallisation from aqueous ethanol gave pure 2:3:4:5-tetraiodopyrrole (85 mg, 3 per cent), m.p. 140–150° (dec.) (Found: C, 8·9; H, 0·4; N, 2·3. Calc. for C_4HNI_4: C, 8·4; H, 0·2; N, 2·5 per cent).

(b) *From 4-iodo-2:6-dimethylphenol to indole.* This reaction was carried out in a manner similar to that described above; turnip peroxidase (31 ml) and hydrogen peroxide (23 ml, 20 volume) were added to indole (1·17 g, 0·01 mole) and 4-iodo-2:6-dimethylphenol[11] (4·96 g, 0·02 mole) in acetate buffer solution (2 l., 0·1 M, pH 4·7). Extraction with ethanol, acetone and ether, followed by chromatography, gave 3-iodoindole (170 mg, 7 per cent), m.p. 71–72° (dec.).

(c) *From 4-iodo-2:6-dimethylaniline to phenol.* Turnip peroxidase (16 ml) and hydrogen peroxide (10 ml, 20 volume) were added during 12 hr to 4-iodo-2:6-dimethylaniline[12] (14·82 g, 0·06 mole) and phenol (1·82 g, 0·02 mole) in phosphate–citrate buffer solution[13] (2 l., pH 5·4). The mixture was then allowed to stand for 14 hr, acidified and extracted exhaustively with ether (250 ml). The ethereal solution was washed with 10% sodium hydroxide solution (5 × 100 ml), and the combined washings were acidified and extracted with ether (6 × 100 ml). The combined ethereal solutions were dried and evaporated; the resulting solid when recrystallised thrice from aqueous ethanol gave 2:4:6-triiodophenol (346 mg, 7·3 per cent), m.p. and mixed m.p. 156°.

(d) *From 4-iodo-2:6-dimethylaniline to p-hydroxyphenylacetic acid.* Turnip peroxidase (72 ml) and hydrogen peroxide (28·5 ml, 20 volume) were added during 31 hr to 4-iodo-2:6-dimethylaniline (12·35 g, 0·05 mole) and *p*-hydroxyphenylacetic acid[14] (0·76 g, 0·005 mole) in phosphate–citrate buffer solution (1 l., pH 5·9). The mixture was made alkaline and filtered. The filtrate was extracted with ether (10 × 50 ml), and the aqueous portion was acidified and extracted with ether (10 × 50 ml). Evaporation of the second ether extract gave a solid (0·916 g), which was dissolved in alkali and reprecipitated with acid. Repeated recrystallisation from aqueous ethanol gave 4-hydroxy-3:5-di-iodophenylacetic acid (545 mg, 27 per cent), m.p. 253–256° (Found: C, 23·7; H, 1·9. Calc. for $C_8H_6O_3I_2$: C, 23·8; H, 1·5 per cent).

(e) *From 4-iodo-2:6-dimethylphenol to tyrosine.* (i) Turnip peroxidase (42 ml) and hydrogen peroxide (27 ml, 20 volume) were added in portions to 4-iodo-2:6-dimethylphenol (4·96 g, 0·02) mole and tyrosine (1·81 g, 0·01 mole) in phosphate–citrate buffer solution (2 l., pH 5·0). Alkali was then added until the solution had pH 7·0, and the mixture was extracted with ether (4 × 250 ml); the aqueous portion was examined by paper chromatography—ascending chromatograms were run overnight on Whatman No. 1 filter-paper, and the dried chromatograms were sprayed with diazotised sulphanilic acid.[15] Two phenolic amino acids were detected and were found to be identical

[11] K. Heicken, *Angew. Chem.* **52**, 263 (1939).
[12] B. M. Roberts, Ph. D. Dissertation Cambridge University (1956).
[13] T. C. McIlvaine, *J. Biol. Chem.* **49**, 183 (1921).
[14] J. H. Wilkinson, *Biochem. J.* **63**, 601 (1956).
[15] E. C. Albright, F. C. Larson and W. P. Deiss, *Proc. Soc. Exp. Biol., N.Y.* **84**, 240 (1953).

with tyrosine (R_F 0·31 ± 0·03 in butan-1-ol–2 N formic acid[4]) and 3-iodotyrosine (R_F 0·55 ± 0·05).

(ii) Peroxidase (41 ml) and hydrogen peroxide (19 ml) were gradually added to tyrosine (0·905 g, 0·005 mole) and 4-iodo-2:6-dimethylphenol (4·96 g, 0·02 mole) in phosphate–citrate buffer solution (2500 ml, pH 5·0). Alkali was now added until the solution had pH 7·4, and the mixture was extracted with ether (4 × 300 ml). Paper chromatography of the aqueous phase revealed the presence of 3-iodotyrosine and 3:5-di-iodotyrosine (R_F 0·65 ± 0·05).

(f) *From 3:5-di-iodotyrosine to thyronine.* Turnip peroxidase and hydrogen peroxide (20 volume) (2·4 ml of each) were added in portions to 3:5-di-iodotyrosine (21·1 mg, 0·05 mmole) and thyronine (10·4 mg, 0·038 mmole) in phosphate–citrate buffer solution (200 ml, pH 5·4). Paper chromatography under the same conditions as before, but with butan-1-ol–6 N ammonia solution[4] as solvent, revealed the presence of 3′-iodothyronine (R_F 0·50 ± 0·03) and thyronine (R_F 0·59 ± 0·03).

(g) *From 3:5-di-iodotyrosine to 3:5-di-iodothyronine.* Turnip peroxidase (1·5 ml), and hydrogen peroxide (1·0 ml, 20 volume) were added to 3:5-di-iodotyrosine (55 mg, 0·13 mmole) and 3:5-di-iodothyronine (4·6 mg, 0·009 mmole) in phosphate–citrate buffer solution (1 l., pH 5·4). The pH of the solution was adjusted to 8·0, and the mixture was examined by paper chromatography as described under (f). Thyroxine (R_F 0·70 ± 0·03) was found to be present in addition to another material (R_F 0·85 ± 0·05), which was probably either 3:5:3′-tri-iodothyronine or 3:5-di-iodothyronine.

Peroxidase-catalysed oxidation of 3-iodotyrosine

Turnip peroxidase (8 ml) and hydrogen peroxide (3·5 ml, 20 volume) were added during 3 hr to 3-iodotyrosine[16] (92 mg, 0·3 mmole) in phosphate–citrate buffer solution (200 ml, pH 5·9); sodium fluoride (2·0 g) was added and the mixture was allowed to stand for 3 hr and was then chromatographed on Whatman No. 1 filter-paper in butan-1-ol–2 N formic acid as in (e) above. Diazotised sulphanilic acid revealed the presence of 3:5-di-iodotyrosine (R_F 0·65 ± 0·03) and of 3-iodotyrosine (R_F 0·55 ± 0·03).

Tetraethyl pyrophosphate from diethyl phosphoroiodidate

Iodine (25·4 g, 0·1 mole) in ether (250 ml) was added at 0° to triethyl phosphite[17] (16·6 g, 0·1 mole) in ether (50 ml). The resulting solution of diethyl phosphoroiodidate was treated at 0° with a mixture of pyridine (7·9 g, 0·1 mole) and water (0·9 g, 0·05 mole). The mixture was warmed to 35° during 20 min, then cooled and filtered and the filtrate was distilled (after removal of solvent under reduced pressure) to give tetraethyl pyrophosphate (6·6 g, 45 per cent), b.p. 135–140°/1 mm. The infra-red absorption spectrum of this material was identical with that of an authentic sample of the pyrophosphate prepared by the method of Toy.[7]

Tricyclohexyl phosphite

A solution of phosphorus trichloride (20·6 g, 0·15 mole) in ether (40 ml) was added during 45 min to a stirred solution of *cyclo*hexanol (45 g, 0·45 mole) and dimethylaniline (55 g, 0·45 mole) in ether (100 ml) at 0°. The mixture was allowed to stand for

[16] R. Pitt-Rivers, *Chem. & Ind.* 21 (1956).
[17] H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.* 380 (1945).

2 hr and it was then filtered; the filtrate was dried (sodium sulphate) and filtered, and then warmed under reduced pressure to remove low-boiling liquids. Distillation of the residual material gave tri*cyclo*hexyl phosphite (35 g, 72 per cent), b.p. 164–165°/0·6 mm as a translucent very deliquescent solid. (Arbuzov and Valitova[18] reported b.p. 175–176°/1 mm for the ester prepared by a different method.)

Iodine (2·54 g, 0·01 mole) in ether (25 ml) was added gradually to a solution of tri*cyclo*hexyl phosphite (3·28 g, 0·01 mole) in ether (25 ml) at 0°; a trace of free iodine was present at the end of the addition. A solution of aniline (1·86 g, 0·02 mole) in ether (10 ml) was now added; a white precipitate of anilinium iodide separated at once. The mixture was filtered and the filtrate was warmed under reduced pressure; the residual material was *di*cyclo*hexyl* N-*phenylphosphoramidate*, which, after recrystallisation from aqueous ethanol, had m.p. 121·5° (Found: C, 64·0; H, 8·6; N, 4·1. $C_{18}H_{28}O_3NP$ requires C, 64·0; H, 8·3; N, 4·2 per cent).

*Conversion of tri*cyclo*hexyl phosphite to di*cyclo*hexyl phosphate*

Tri*cyclo*hexyl phosphite (6·29 g, 0·019 mole) in light petroleum (40 ml, boiling range 60–80°) was added during 40 min to a mixture of *cyclo*hexylamine (3·8 g, 0·038 mole), acetic acid (3·8 ml), iodine (4·90 g, 0·019 mole) and potassium iodide (20 g) in water (200 ml) and light petroleum (200 ml). After a further 45 min the layers were separated and the organic layer was washed with hydrochloric acid and then with water. Removal of solvent gave a nitrogen-free oil, which crystallised slowly on standing. Recrystallisation from aqueous ethanol gave di*cyclo*hexyl hydrogen phosphate (1·55 g, 31 per cent), m.p. 80–81° (Found: C, 55·5; H, 8·9. Calc. for $C_{12}H_{23}O_4P$: C, 55·0; H, 8·8 per cent).

Conversion of triethyl phosphite to tetraethyl pyrophosphate by the peroxidase system

(i) Horse-radish peroxidase was added in portions to a stirred, cooled mixture of potassium iodide (25·72 g, 0·155 mole), barium peroxide (13·13 g, 0·0775 mole), acetate buffer (4·20 ml, 1 M, pH 4·7), triethyl phosphite (12·86 g, 0·0775 mole) and pyridine (6·27 g, 0·08 mole) in light petroleum (100 ml, boiling range 60–80°). After 2 hr the mixture was filtered and the filtrate was warmed under reduced pressure to remove low-boiling liquids. Distillation of the residual liquid gave tetraethyl pyrophosphate (1·24 g, 11 per cent), b.p. 125–130°/0·5 mm.

(ii) A second experiment was carried out, essentially as in (i); double quantities of reactants were used, but with omission of pyridine. A yield of 1·58 g, 7 per cent of tetraethyl pyrophosphate was obtained.

*Conversion of di*cyclo*hexyl phosphite to di*cyclo*hexyl phosphate*

Turnip peroxidase (10 ml) and hydrogen peroxide (2 ml, 20 volume) were added gradually to di*cyclo*hexyl phosphite[19] (0·78 g, 0·0032 mole) and iodine (0·40 g, 0·0016 mole) in ether (20 ml) and acetate buffer solution (30 ml, 0·33 M, pH 4·7). After 100 min the layers were separated, and aniline (0·56 g, 0·0032 mole) in ether (10 ml) was added to the organic layer; needles of *anilinium di*cyclo*hexyl phosphate*

[18] A. E. Arbuzov and F. G. Valitova, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk* 801 (1952).
[19] H. G. Cook, J. D. Ilett, B. C. Saunders, G. J. Stacey, H. G. Watson, I. G. E. Wilding and S. J. Woodcock, *J. Chem. Soc.* 2921 (1949).

(0·70 g, 61 per cent) separated (Found: C, 60·7; H, 8·7; N, 3·8. $C_{18}H_{33}O_4NP$ requires C, 60·9; H, 8·4; N, 3·9 per cent).

Conversion of dibenzyl phosphite to dibenzyl phosphate

Turnip peroxidase (18 ml) and hydrogen peroxide (6 ml, 20 volume) were added during 3 hr to dibenzyl phosphite (2·62 g, 0·01 mole) and iodine (0·254 g, 0·001 mole) in ether (100 ml) and acetate buffer solution (100 ml, 0·1 M, pH 4·7). The layers were separated and the aqueous portion was washed with ether (4 × 25 ml). The combined organic layers were evaporated to dryness and the residual material recrystallised from a mixture of chloroform and pentane to give dibenzyl hydrogen phosphate (0·93 g, 33 per cent), m.p. 78–80° (Found: C, 60·2; H, 5·4. Calc. for $C_{14}H_{15}O_4P$: C, 60·4; H, 5·6 per cent).

Peroxidase-induced formation of diethyl N*-phenylphosphoramidate from triethyl phosphite*

Horse-radish peroxidase (21·1 ml, P.N. 5) and hydrogen peroxide (6 ml, 20 volume) were added during 9 hr to 3:5-di-iodotyrosine (3·009 g, 0·007 mole) in acetate buffer (4 l., 0·1 M, pH 4·7). The mixture was allowed to stand for 14 hr and it was then extracted with ether (5 × 200 ml). The combined ether layers were added to a cooled solution of triethyl phosphite (0·208 g, 1·25 mmoles) in ether (50 ml); aniline (0·233 g, 2·5 mmole) in ether (10 ml) was added to the resulting mixture, whereupon a precipitate of anilinium iodide rapidly separated. The mixture was filtered and the filtrate was evaporated to dryness to give diethyl N-phenylphosphoramidate (150 mg), m.p. 96°.

Conversion of diethyl phosphite to tetraethyl pyrophosphate in the presence of peroxidase.

Horse-radish peroxidase (1·5 ml, P.N. 500) and hydrogen peroxide (12·0 ml, 100 volume) were added during 12 hr to a stirred cooled solution of diethyl phosphite (13·80 g, 0·1 mole) and iodine (2·54 g, 0·01 mole) in dioxan (100 ml). The mixture was left at 0° for a further 12 hr and it was then filtered through sodium sulphate, and the filtrate was warmed under reduced pressure to remove volatile liquids. The residual material was distilled to give TEPP (1·54 g, 5 per cent), b.p. 125–130°/0·5 mm.

Conversion of diethyl phosphite to TEPP in the presence of pyridine

A solution of iodine (30·6 g, 0·12 mole) in ether (300 ml) was added with stirring during 2 hr to a solution of diethyl phosphite (15·66 g, 0·12 mole), pyridine (18·96 g, 0·24 mole) and water (1·08 g, 0·06 mole) in ether (70 ml) at 0°. The mixture was then warmed to 35° during 30 min and then cooled to 0° and filtered. The filtrate was warmed under reduced pressure and the residual liquid was distilled to give tetraethyl pyrophosphate (7·87 g, 46 per cent), b.p. 129–311°/0·35 mm.

Preparation of phosphoramidates from diethyl phosphite

A solution of iodine (5·1 g, 0·02 mole) in ether (50 ml) was added during 15 min to a stirred cooled solution of diethyl phosphite (2·76 g, 0·02 mole) and pyridine (1·58 g, 0·02 mole) in ether (30 ml). The mixture was kept at 0° for a further 15 min and then filtered. The filtrate was treated with a solution of aniline (3·72 g, 0·04 mole) in ether

(10 ml) and the mixture was allowed to stand for 3 hr and then filtered. The filtrate was washed with water, sodium hydroxide solution, water, hydrochloric acid and water again, and finally evaporated. The white solid thus obtained was recrystallised from aqueous ethanol to give diethyl N-phenylphosphoramidate (2·98 g, 65 per cent), m.p. 96° (McCombie *et al.*[17] reported m.p. 95·5–96·5°).

A solution of iodine (5·1 g, 0·02 mole) in ether (50 ml) was added during 45 min to a solution of benzylamine (6·42 g, 0·06 mole) and di*tert.*-butyl phosphite[20] (3·88 g, 0·02 mole) in ether (30 ml). After 1 hr the mixture was filtered and the filtrate was washed, evaporated and recrystallised as described above to give di*tert.*-butyl N-benzylphosphoramidate (2·45 g, 41 per cent), m.p. 96–98° (Goldwhite and Saunders[20] reported m.p. 97–98°).

Peroxidase-catalysed oxidation of cysteine

Cysteine hydrochloride (158 mg, 0·001 mole) and 3:5-di-iodotyrosine (217 mg, 0·0005 mole) were dissolved in acetate buffer solution (500 ml, 0·1 M, pH 4·7); turnip peroxidase (8 ml) and hydrogen peroxide (3 ml, 2 volume) were added during 2 hr. A precipitate of almost pure cystine (102 mg, 85 per cent) separated, which was chromatographically identical with an authentic sample. A trace of free iodine was present at the end of the experiment. Omission of iodine donor gave a much slower oxidation, while omission of enzyme or of both enzyme and di-iodotyrosine led to very slow reaction.

Acknowledgements—One of us (B. P. S.) is indebted to the Department of Scientific and Industrial Research for a maintenance allowance.

[20] H. Goldwhite and B. C. Saunders, *J. Chem. Soc.* 2409 (1957).

Tetrahedron, 1958, Vol. 4, pp. 178–185. Pergamon Press Ltd., London

THE 1,1,2,3,4,5,6-HEPTAMETHYLBENZENONIUM ION

W. VON E. DOERING, M. SAUNDERS
Sterling Chemistry Laboratory, Yale University, New Haven, Conn.

H. G. BOYTON, H. W. EARHART, E. F. WADLEY, W. R. EDWARDS
Humble Oil and Refining Co., Baytown, Texas

and

G. LABER
Hickrill Chemical Research Foundation Inc., Katonah, N.Y.

(*Received* 28 *April* 1958)

Abstract—The terminal product in the Friedel and Crafts methylation of benzene and its methyl homologues is 1,1,2,3,4,5,6-heptamethylbenzenonium ion (I), a new comparatively stable carbonium ion. The ion decomposes slowly in aqueous acid to methanol and hexamethylbenzene (III) and can be synthesized from these products by treatment with sulfuric acid. (I) is in rapidly reversible equilibrium with a proton and a neutral molecule, $C_{13}H_{20}$ to which the structure 4-methylene-1,1,2,3,5,6-hexamethyl*cyclo*hexadiene-2,5 (II) has been assigned.

THE catalyst in reactions of the Friedel and Crafts type often becomes inactive after a relatively short time. In the methylation of benzene and its methyl homologues with methyl chloride and aluminum chloride at 80°,[1] deactivation sets in rapidly with the consumption of relatively large quantities of catalyst. In this paper the major cause of the loss of catalyst activity is uncovered.

To find out whether organic substances might be inactivating the catalyst, aliquots from the upper and lower phases of the reaction mixture were removed at intervals during the methylation. After being washed with water, these samples were examined by low-voltage mass-spectrographic analysis.[2] In the upper hydrocarbon layer, the expected increase in concentration of the higher methylated homologues through hexamethylbenzene was observed. In the dense, lower, liquid layer, which contained all the aluminum chloride, substances corresponding to mass 176 developed rapidly and reached a high concentration (ca. 40 per cent) by the time the catalyst was no longer active. In addition there was a high concentration (relative to the upper layer) of penta- and hexa-methylbenzene, consistent with the greater basicity of these hydrocarbons.[3]

The remarkable mass number 176 corresponds to $C_{13}H_{20}$ and is consistent with the hypothesis that one more carbon atom (CH_2) has been added to hexamethylbenzene (162). Whatever the detailed structure may be, it is immediately evident that the substance responsible for the 176 mass number must be more basic than hexamethylbenzene, since it is present only in the lower layer. By taking advantage of the fact that the new substance is indeed so basic as to be extractable from pentane

[1] C. Friedel and J. M. Crafts, *C. R. Acad. Sci., Paris* **84**, 1392 (1877); *Ann. Chim. Phys.* (6) **1**, 449 (1884); O. Jacobsen, *Ber. Dtsch. Chem. Ges.* **14**, 2624 (1881); L. I. Smith and F. J. Dobrovolny, *J. Amer. Chem. Soc.* **48**, 1413 (1926).
[2] F. H. Field and S. H. Hastings, *Analyt. Chem.* **28**, 1248 (1956).
[3] D. A. McCauley and A. P. Lien, *J. Amer. Chem. Soc.* **73**, 2013 (1951).

with aqueous hydrochloric acid of concentration higher than 4 N, a crystalline hydrocarbon, $C_{13}H_{20}$, m.p. 47°, can be isolated easily in a pure state. By contrast, hexamethylbenzene is insoluble even in concentrated hydrochloric acid.

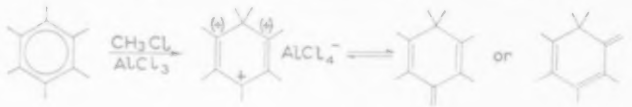
The basicity of the $C_{13}H_{20}$ hydrocarbon (II) is due to the remarkable stability of the conjugate acid, $C_{13}H_{21}^+$ (I). This ion can be obtained as the crystalline $AlCl_4^-$ salt, either by treating pure (II) with hydrogen chloride and aluminum chloride or, directly, from the lower layer of the methylation reaction by crystallization. In the usual organic chemical manipulations, it appears that the reversible addition and loss of proton is very rapid.

The $C_{13}H_{21}^+$ ion is the major catalyst poison. As a stable carbonium ion, it liberates, in effect, an equimolar quantity of chloride ion, which binds aluminum chloride tightly as the catalytically inactive aluminum tetrachloride ion. In fact, the methylation of trimethylbenzenes is

$$\underset{(II)}{C_{13}H_{20}} + HCl \rightleftharpoons \underset{(I)}{C_{13}H_{21}^+} + Cl^- + AlCl_3 \longrightarrow AlCl_4^-$$

stopped by adding the $C_{13}H_{20}$ hydrocarbon and hydrogen chloride in amounts equivalent to slightly more than the aluminum chloride catalyst.

The task of determining the structure of the hydrocarbon and its conjugate acid



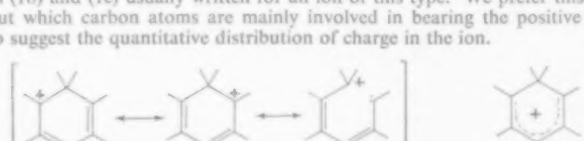
III I IIa IIb

was lightened by considering *a priori* the mechanistically reasonable paths open to the reactants. For the $C_{13}H_{21}^+$ ion, structure (I) appeared likely, whence the $C_{13}H_{20}$ hydrocarbon would have either structure (IIa) or (IIb).*

On standing for days, a solution of the $C_{13}H_{21}^+$ ion (I) in aqueous hydrochloric acid deposits crystals of hexamethylbenzene (III) and produces methanol, as evidenced by the development of a peak in the nuclear magnetic resonance (n.m.r.) spectrum corresponding in position to that shown by methanol in aqueous acid of identical strength. Reversely, (I) can be synthesized by treating hexamethylbenzene with methanol and concentrated sulfuric acid at 95°. These observations are certainly consistent with the seven methyl groups and six-membered ring of structure (I).

In the $C_{13}H_{20}$ hydrocarbon there is strong evidence for the presence of only two vinyl hydrogens, in the form of a methylene group. The n.m.r. spectrum in carbon

* (I) is a shorthand notation in which the two positive charges in parentheses represent the two other resonance structures (Ib) and (Ic) usually written for an ion of this type. We prefer this notation to (Ie)[4] because it points out which carbon atoms are mainly involved in bearing the positive charge. Neither notation is meant to suggest the quantitative distribution of charge in the ion.



Ib Ic Id Ie

[4] M. J. Dewar, *The Electronic Theory of Organic Chemistry* pp. 162–176. Oxford University Press, London (1949).

tetrachloride solution (Fig. 1) shows three peaks located at 70, 189 and 216 cycles per second (relative to benzene hydrogens). Their intensities have been determined by operating with a rapid-sweep[5] technique and correspond to 2·0, 6·5 and 11·5 hydrogen atoms, respectively (after normalization to a total of 20). The 70 c/s peak corresponds in position to that indicated for vinyl hydrogen.[6] In the infrared spectrum of (II) there is a strong band at 855 cm^{-1} suggestive of an asymmetrically

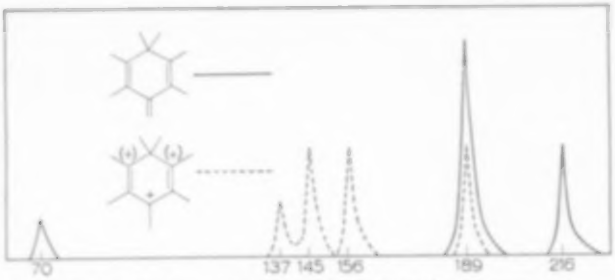


FIG. 1. Nuclear magnetic resonance in c/s from benzene.

disubstituted olefin ($CH_2 = C$). Finally, the presence of the methylene group is confirmed by the formation of formaldehyde in the ozonolysis of (II).

The other two peaks in the n.m.r. spectrum of (II) are accommodated by the remaining methyl groups. The position of the 216 c/s peak of relative intensity 6·5 is consistent with the presence of the geminate dimethyl group. Paraffinic methyl hydrogen absorbs at higher fields than vinyl methyl, although the exact position of such peaks is strongly dependent on the conditions of measurement.[7] Confirmation of the geminate dimethyl group is to be found in the presence of two bands at 1359 and 1380 cm^{-1} in the infrared spectrum[8] of (II). The remaining peak at 189 c/s and relative intensity 11·5 reflects the four vinyl methyl groups hypothesized in structure (II). It may be remarked that the singlet character of the 189 and 216 c/s peaks is incompatible with their origin in ethyl or *iso*propyl groups, which always appear as multiplets.[9]

The ultraviolet spectrum of (II) (Fig. 2) shows a maximum at 257 mμ (log ϵ 4·27) indicative of a conjugated system containing at least two double bonds. The maximum lies at too low a wave length to be consistent with the fully conjugated system in structure (IIb). For such a system of three double bonds the calculated maximum absorption is at 318 mμ.[10] For a cross-conjugated system of type (IIa) insufficient analogies are available to permit estimation of the position of maximum absorption. It might reasonably be expected to lie beyond 239 mμ, the value expected of the related conjugated diene. A further argument supporting (IIa) can be based on the singlet character of the 70 c/s peak. In structure (IIb) the two hydrogens of the exocyclic methylene group are quite differently situated and might be expected to suffer different degrees of chemical shift, with a resultant increase in the complexity of absorption in the vinyl hydrogen region.

[5] Cf. R. B. Williams, *Ann. N. Y. Acad. Sci.* **70**, 890 (1958).
[6] L. H. Meyer, A. Saika and H. S. Gutowsky, *J. Amer. Chem. Soc.* **75**, 4567 (1953).
[7] A. A. Bothner-By and R. E. Glick, *J. Chem. Phys.* **26**, 1651 (1957).
[8] N. Sheppard and D. M. Simpson, *Quart. Rev. Chem. Soc.* **7**, 19 (1953).
[9] R. E. Glick and A. Bothner-By, *J. Chem. Phys.* **25**, 362 (1956).
[10] L. Dorfman, *Chem. Rev.* **53**, 47 (1953).

The available data is therefore consistent with the *cross-conjugated* structure, 4-methylene-1,1,2,3,5,6-hexamethyl*cyclo*hexadiene-2,5 (IIa). The molecule is accordingly the terminal completely methylated homologue in the semibenzene series studied by von Auwers and Ziegler.[11] The lack of ultraviolet spectral data in their work precludes comparison with the spectrum of (II). All the examples synthesized by von Auwers suffered rapid rearrangement to the related isomeric benzene on treatment with acid. Such an aromatizing rearrangement is structurally impossible in (II). As a consequence, (II) is much more stable in acid than any of its lower homologues.

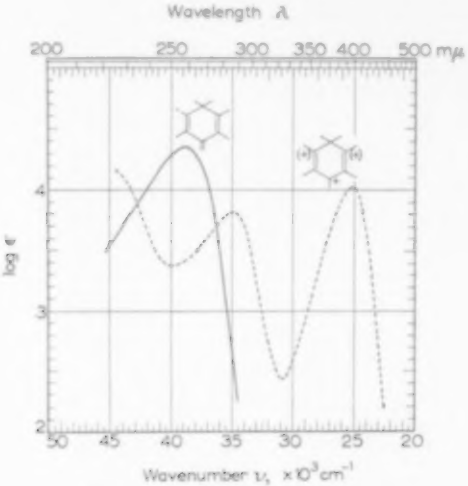


FIG. 2. Ultraviolet spectrum of (II).

The structure of the conjugate acid (I) of the semibenzene (II) is most clearly elucidated from the change in n.m.r. spectrum which occurs when (II) is converted to (I) in concentrated hydrochloric acid. The spectrum (Fig.1) now consists of four peaks at 137, 145, 156 and 189 c/s with relative intensities corresponding to 3, 6, 6 and 6 hydrogen atoms, respectively, when normalized to a total of 21. The most significant change is the disappearance of the 70 c/s peak corresponding to the exocyclic methylene group and its replacement by the 137 peak of a methyl group. In structure (I) the 4-methyl group is unique, whereas the other types appear in pairs. The down-field shift suffered by the 4-methyl group is relatively large and is almost certainly caused by the positive charge in the ion. Consequent on the effect of this charge, the four vinyl methyl groups appearing at 189 c/s in (II) are split into two pairs in (I). The partial positive charge on carbon atoms 2 and 6 draws the two methyl groups at these positive positions down-field, leaving the 3- and 5-methyl groups less affected. The peak at 145 c/s in the n.m.r. spectrum of (I) is therefore assigned to the 2- and 6-methyl groups, while that at 156 c/s originates in the 3- and 5-methyl groups. Finally, the peak at 189 c/s must be ascribed to the geminate dimethyl group. Because of the unpredictable and probably large difference to be expected between carbon tetrachloride and concentrated hydrochloric acid as solvents, one cannot evaluate quantitatively the effect of the positive charge on the position

[11] K. von Auwers and K. Ziegler, *Liebigs Ann.* **425**, 217 (1921).

of the geminate dimethyl peak. However, it is noteworthy that the 4-methyl has been shifted more than the 2, 6-pair. A dispersion of charge by no-bonded structures of the type Id may be responsible.

For the $C_{13}H_{21}^+$ ion the structure 1,1,2,3,4,5,6-heptamethylbenzenonium* ion is accordingly preferred. The possibility that I have the structure of a Dewar "π-complex" (Iα) cannot be rejected on the basis of present evidence. The hexagonally

Iα Iβ

symmetrical structure, (Iβ), considered in passing as a model for the "π-complex",[17] requires an n.m.r. spectrum of two peaks of relative intensity ratio 3:18. The observed spectrum being completely inconsistent with this prediction, structure (Iβ) is rigorously excluded. This result is relevant to the general problem of benzene complexes of the $C_6H_6 \cdot A^+$ type.[18] In the near future it is hoped to present evidence to show that structures (I) and (Iα) are quite close in energy. The isolation of the $C_{13}H_{21}^+$ ion offers the first significant opportunity to distinguish between the two structures by X-ray crystallographic analysis. Such an investigation is already under way.

The ultraviolet spectrum of (I) (Fig. 2) [λ_{max} 287 mμ(log ϵ 3·83), λ_{max} 397 mμ (log ϵ 3·93)] extends into the visible, causing solutions of the ion to be yellow. These

* The system, $C_6H_7^+$ (A), and its derivatives, have been named variously phenonium ion [D. J. Cram, *J. Amer. Chem. Soc.* **74**, 2129 (1952)], benzenium ion [12] and σ-complex.[13] In naming the system it is desirable to provide for unequivocal numerical designations of substituents and to allow for the existence of the related cationic fragments, $C_6H_6^+$ (B) [S. I. Weissman, E. de Boer and J. J. Conradi, *J. Chem. Phys.* **26**, 963 (1957)] and $C_6H_5^+$ (C). "Phenonium" has been widely used in discussions of certain anchimerically assisted displacements and Wagner–Meerwein rearrangements and is perhaps best reserved for this purpose (see particularly footnote 6 in Muller *et al.*[15]). "σ-complex" is acceptable as a generic term, but is otherwise

A B C D E

useless. "Benzenium", although formally acceptable, is so obviously the appropriate designation for the molecule ion, $C_6H_6^+$ (B) (e.g., anthracenium) that we consider it most unfortunate that Muller and co-workers should have diverted the word to the use of $C_6H_7^+$. We would like to urge the adoption of "benzenonium" (napthalenonium, pyrenonium, etc.). The suffix "onium" appropriately connotes the introduction of positive charge by the *addition* of a Lewis acid (H^+, R^+, Br^+, etc.) and therefore finds analogy in ammonium, oxonium and the like. ("Benzonium" was considered and rejected because of the inappropriate implications of the term "benz".) The usual numbering systems are applicable without change and the designation of the position of a hydrogen can be accomplished by a system already well established [cf. *Chem. Abstr.* **39**, 5932 (1945)]. Thus the molecules D and E acquire the names 1(1), 3,5- and 1(2), 3,5-trimethylbenzenonium, respectively, in which the number in parenthesis designates the carbon atom which is quadrivalent by virtue of having at least one of its two extracyclic substituents be an hydrogen atom.

[12] N. Muller, L. W. Pickett and R. S. Mulliken, *J. Amer. Chem. Soc.* **76**, 4770 (1954).
[13] H. C. Brown and J. D. Brady, *J. Amer. Chem. Soc.* **74**, 3570 (1952).
[14] M. J. S. Dewar, *J. Chem. Soc.* 777 (1946).
[15] M. J. S. Dewar, *Disc. Faraday Soc.* **2**, 50 (1947).
[16] M. J. S. Dewar, *Bull. Soc. Chim. Fr.* [5], **18**, c71 (1951).
[17] C. A. Coulson and M. J. S. Dewar, *Disc. Faraday Soc.* **2**, 54 (1947).
[18] R. E. Rundle and J. D. Corbett, *J. Amer. Chem. Soc.* **79**, 757 (1957); see other pertinent references therein.

maxima are in felicitous agreement with those reported by Reid[19] for the benzenonium ions obtained from alkyl-substituted benzenes in liquid hydrogen fluoride and boron trifluoride. 1,2,3,4,5,6-Hexamethylbenzenonium ion, for example, shows λ_{max} 283 mμ (log ϵ 4·31) and λ_{max} 401 mμ (log ϵ 4·42), while 1(2),3,5-trimethylbenzenonium ion (E) shows λ_{max} 391 mμ (log ϵ 4·43). It is gratifying to find these protium antecedents of (I) having closely similar spectra. Because of the ease with which they lose protons, their isolation in crystalline state has been accomplished only recently in the distinctive work of Oláh and Kuhn.[20]

In Wheland's original quantum mechanical analysis of aromatic substitution[21] and in Dewar's[22] extension of this approach the benzenonium ion structure was used to represent the transition state. Since that time, the work of Melander on the mechanism of other aromatic substitutions,[23] that of McCauley and Lien[24] and H. C. Brown and Brady[13] specifically in the Friedel–Crafts reaction and finally the above-mentioned isolation by Oláh[20] have made it clear that the benzenonium geometry in fact represents an intermediate. The discovery of (I) demonstrates even more convincingly that the benzenonium structure can be an energy minimum, if additional evidence were any longer necessary. The possibility nevertheless remains that cases may arise in which this geometry corresponds to a transition state rather than an intermediate. The present case is an especially favorable one in that three tertiary carbonium ion forms (Ia, b and c) contribute to the stabilization of the ion, whereas the unsubstituted benzenonium ion is represented by three higher-energy secondary forms.

EXPERIMENTAL

Preparation of crude 1,1,2,3,4,5,6-*heptamethylbenzenonium aluminum tetrachloride* (I). The exhaustive methylation was carried out in a 5 l. three-necked flask equipped with stirrer, thermometer and gas inlet and outlet lines. To 1200 g of mixed trimethylbenzenes at 37° and 1093 g of powdered anhydrous aluminum chloride, methyl chloride was passed in below the liquid surface with vigorous agitation. The contents were heated quickly to 80° and methyl chloride was passed in at a rate of 650 g/hr for 8 hr, when the production of hydrogen chloride ceased. The dark-red liquid product was poured from the flask into a closed storage vessel where it crystallized below 80°.

When the crushed crude salt was treated with toluene at room temperature, two liquid layers formed: an upper layer having a purple fluorescence, which was decanted and discarded; and a very dark lower layer, from which dark crystals were precipitated on diluting with pentane. The solvent was decanted and the crystals were dried *in vacuo*. When the crystals were dissolved in dry ethyl acetate at 40°, a dark green solution was obtained, from which some insoluble material was removed by centrifuging and pipetting, an operation carried out twice. On cooling in ice and scratching, cooling further to −60° and finally filtering by centrifuging at −60°, greenish needles were obtained. A second crystallization gave bright-yellow needles, which were washed first with 1:1 ethyl acetate–pentane and then with pentane, with

[19] C. Reid, *J. Amer. Chem. Soc.* **76**, 3264 (1954).
[20] G. Oláh and S. Kuhn, *Nature, Lond.* **178**, 1344 (1956).
[21] G. Wheland, *J. Amer. Chem. Soc.* **64**, 900 (1942).
[22] M. J. S. Dewar, *J. Chem. Soc.* 463 (1949).
[23] L. Melander, *Arkiv Kemi* **2**, 211 (1950).
[24] D. A. McCauley and A. P. Lien, *J. Amer. Chem. Soc.* **74**, 6246 (1952); *Ibid.* **75**, 2411 (1953); *Ibid.* **76**, 2354 (1954).

filtering each time by centrifuging. The material was dried *in vacuo* and stored at −60° excluding moisture (Found: C, 45·2; H, 6·1, Al, 7·9; Cl, 41·0. $C_{13}H_{21}AlCl_4$ requires C, 45·1; H, 6·1; Al, 7·8; Cl, 41·0 per cent)

4-*Methylene*-1,1,2,3,5,6-*hexamethyl*cyclo*hexadiene*-2,5 (II). A 43·3 g portion of the crushed crude salt of (I) was extracted in a Soxhlet apparatus with pentane for 2 hr. Concentration of the pentane solution afforded 3·71 g (8·5 per cent) of crude hexamethylbenzene (III). Sublimation at 12 mm and 60° followed by two recrystallizations from ethanol gave pure (III), m.p. 165·5–166·5°, which showed no depression on admixture with an authentic sample (obtained from Distillation Products), m.p. 166°.

The unextracted material was hydrolyzed with 300 ml of ice-cold water and extracted with two 200 ml portions of pentane. The combined pentane solutions were extracted with 30 ml portions of concentrated hydrochloric acid. The combined acid solutions were poured into 800 ml of ice-cold water, neutralized with sodium bicarbonate and extracted with pentane. The dried (anhydrous sodium sulfate) pentane solution was concentrated to 11·05 g (50 per cent) of a dark-yellow oil, which crystallized with ease. The infrared spectrum of this material is identical in all but the smallest detail with the spectrum of pure (II), m.p. 46·5–47·5°, obtained by three recrystallizations from methanol. Colorless material is most easily obtained by preceding the crystallization with one vacuum sublimation (Found: C, 88·0; H, 11·7. $C_{13}H_{20}$ requires C, 88·6; H, 11·4 per cent). The compound is so sensitive to air that special care is needed to obtain an analysis in which the carbon value is not 2–3 per cent low.

The ultraviolet spectrum was measured in a Beckman DU spectrometer in *iso*-octane solution: λ_{max} 257 mμ (log ϵ 4·27).

(II) is quite unstable in air, being converted in a few hours at room temperature to a brown oil showing a carbonyl and an hydroxyl group in its infrared spectrum. It reacts immediately with bromine and somewhat more slowly with potassium permanganate, and is completely insoluble in water, but dissolves easily in hydrochloric acid more concentrated than 4 N or aqueous acids of comparable strength to give solutions of (I). The ultraviolet spectrum of (II) in concentrated hydrochloric acid [(I) chloride] shows λ_{max} 287 mμ (log ϵ 3.83) and λ_{max} 397 mμ (log ϵ 3·93). (II) is precipitated from aqueous acid solutions of (I) chloride simply on dilution with water. Turbidity is noticed at concentrations below 3 N.

Ozonolysis of (II). After ozone had been passed into a solution of 2.5 g of (II) in 75 ml of ethyl acetate at −78° for 1½ hr, the absorption became very slow, so the reaction was stopped and the solution was concentrated to 15 ml. An aliquot portion of 1·5 ml was shaken with 35 ml of N hydrochloric acid and 0·75 g of zinc dust for 15 min. To the hot filtered solution 5 ml of hot saturated dimedone and enough sodium acetate to bring the pH to 3 were added. A fine crystalline precipitate of the *formaldehyde derivative of dimedone*, (72 mg) m.p. 188–190°, was obtained.

Conversion of (I) *to hexamethylbenzene* (III). After 24 hr at room temperature the crystalline material which had precipitated from a solution of 298 mg of (II) in 15 ml of concentrated hydrochloric acid was extracted with pentane. Washing the pentane layer with aqueous sodium bicarbonate and concentrating gave a brown residue, from which 8 mg of colourless crystals sublimed at 12 mm and 50°. After two recrystallizations from ethanol, hexamethylbenzene, m.p. 166°, was obtained. Over a 3-week period a total of 166 mg of (III) was isolated.

A similar solution of (II) in hydrochloric acid developed a new peak in the n.m.r. spectrum on standing. This band was located at the same position as that shown by a solution of methanol in concentrated hydrochloric acid.

Synthesis of heptamethylbenzenonium ion (I) *from hexamethylbenzene* (III). A total of 218 mg of hexamethylbenzene (III) was added in small portions over a period of 1 hr to a solution of 20 ml of methanol in 100 ml of concentrated sulfuric acid at 95°. After 2 hr, the reaction mixture was cooled, poured on to 750 g of ice, neutralized first with sodium carbonate and finally with sodium bicarbonate and then extracted with 25 ml of pentane. The pentane layer was then extracted with three 3·5 ml portions of concentrated hydrochloric acid; the aqueous extract was neutralized with sodium bicarbonate and extracted with pentane; from the pentane layer, 17 mg of a brown oil was obtained. One crystallization from methanol furnished 5·5 mg of (II), m.p. 45–46°. The infrared spectrum was superimposable on that of the previously obtained (II).

Nuclear magnetic resonance spectra. All n.m.r. spectra were determined with the Varian Associates model 4300 V high-resolution spectrometer with super-stabilizer at 40·01 mc, with use of a spinning sample. Peak positions were measured relative to a benzene capillary by using the sideband superposition technique. Relative numbers of hydrogens were determined by a modified fast-passage technique.

Tetrahedron, 1958, Vol. 4, pp. 186–196. Pergamon Press Ltd., London

THE CONDENSATIONS OF POLYHYDRIC ALCOHOLS AND MONOSACCHARIDES WITH *CYCLO*PENTANONE AND *CYCLO*HEXANONE

V. M. Mićović and Miss A. Stojiljković
Institute of Chemistry, Faculty of Science, University of Belgrade, Yugoslavia

(*Received* 14 *February* 1958)

Abstract—*cyclo*Pentanone and *cyclo*hexanone have been shown to condense with polyhydric alcohols and monosaccharides to yield di- and tri-*cyclo*pentylidene and *cyclo*hexylidene derivatives. Series of new compounds with glycerol, pentaerythritol, *meso*erythritol, arabitol, mannitol, sorbitol, xylose, arabinose, glucose, mannose and fructose have been prepared and characterised. In some instances attempts have been made to prove the structures of the products obtained or to give some experimental evidence for the already proposed structures.

In 1895 Fischer[1] and Speier[2] discovered a new class of sugar derivatives by condensing polyhydroxy compounds with acetone. Since then, these compounds have been employed for purification, isolation and characterisation of polyhydric alcohols and monosaccharides and also as intermediates in the syntheses of partially substituted compounds. Recently, the importance of cyclic ketals and acetals has increased especially in connexion with constitution and configuration of these compounds, i.e. with the size, position and stability of the ketal and acetal rings formed in the course of these condensations.

We have attempted to condense *cyclo*pentanone and *cyclo*hexanone with polyhydroxy compounds with the intention of finding out the possibility of correlating these compounds with already known and well defined acetone derivatives, and in order to see if these compounds would be more convenient than acetone derivatives either for the identification or for the syntheses of polyhydroxy compounds.

The condensations of ketones with polyhydroxy compounds are usually carried out in acid media and in the presence of some dehydrating agent.[3] First, the hemiketal is formed, followed by subsequent ring closure with elimination of 1 molecule of water. The course of the reaction depends to a large extent upon the configuration of the compounds involved in the condensations. The optimum conditions are found when the hydroxy groups are in *cis* positions in Fischer's projection formulae, i.e. when the distance between two oxygen atoms is 2·51 Å. With increasing distance the tendency for cyclic acetal and ketal formation decreases. It seems likely that there exists a parallel between the formation of cyclic ketals and glycolic complexes with boric acid.[4]

[1] E. Fischer, *Ber. Dtsch. Chem. Ges.* **28**, 1167 (1895).
[2] A. Speier, *Ber. Dtsch. Chem. Ges.* **28**, 2531 (1895).
[3] E. Fischer and E. Pfühler, *Ber. Dtsch. Chem. Ges.* **53**, 1606 (1920); R. Dworzak and K. Hermann, *Mh. Chem.* **52**, 83 (1929); H. O. L. Fischer and C. Trabue, *Ber. Dtsch. Chem. Ges.* **60**, 485 (1927); H. Baer and H. O. L. Fischer, *Ber. Dtsch. Chem. Ges.* **63**, 1749 (1930); L. Smith and J. Lindberg, *Ber. Dtsch. Chem. Ges.* **64**, 505 (1931); M. M. Maglio and C. A. Beirger, *J. Amer. Chem. Soc.* **68**, 529 (1946); H. Hibbert and J. Morazain, *Canad. J. Res.* **2**, 35 (1930); *Chem. Abstr.* **24**, 2108 (1930); E. Salmi, *Ber. Dtsch. Chem. Ges.* **71B**, 1803 (1938); A. Dupire, *C. R. Acad. Sci., Paris* **214**, 359 (1942).
[4] J. Boesecken, *Rec. Trav. Chim. Pays-Bas* **40**, 553 (1921); J. Boesecken, *Ber. Dtsch. Chem. Ges.* **56**, 2411 (1923); Chr. Maan, *Rec. Trav. Chim. Pays-Bas* **48**, 332 (1929).

The direct condensation of polyhydroxy compounds with ketones affords five-membered cyclic ketals, substituted dioxolane rings; in the condensations with aldehydes, six-membered acetal rings are formed. The formation of rings of different size has been explained with the help of the Ingold–Thorpe theory.[5] Later, Hann and Hudson[6] and Barker and Bourne[7] presented rules enabling the prediction of the course of condensation of polyhydric alcohols with aldehydes. These rules, based exclusively upon experimental evidence, have been explained on the assumption that polyhydric alcohols have a planar zigzag conformation,[8] with hydroxy groups having positions considerably different from the apparent positions in Fischer's projection formulae. From these rules it could be concluded that the formation of those rings requiring the least deformation of the planar conformations would be mostly favoured. From the point of view of conformational analyses of the (six-membered) cyclic compounds formed, those rules are in full agreement with the general principles of conformational stabilities. However, they cannot be applied to cyclic ketals. That was one of the reasons why we began to study the condensations of polyhydroxy compounds with cyclic ketones.

Many facts indicate the size of the ring to be an important factor in the chemical behaviour of cyclic compounds. According to the I-strain theory[9] and the proposed generalisation for the *exo* and *endo* double bonds[10] in five-and six-membered ring systems, one might expect *cyclo*hexanone to be more reactive than *cyclo*pentanone. Some evidence that this is the case can be found in published papers and is also offered in the present work. However, the size of the ketal rings formed is not in accordance with the theory mentioned above; this fact can be explained only by assuming that the I-strain is not the dominating factor in these condensations.

Condensations of polyhydric alcohols with cyclo*pentanone and* cyclo*hexanone*

Almost all open-chain polyhydric alcohols have been condensed with acetone, but the structures of the products obtained have only been determined in the case of glycerol,[11] xylitol,[12] sorbitol,[13], iditol,[14] mannitol[15] and dulcitol[16] (the information available for xylitol is contradictory). All these condensations afforded five-membered ketal rings, whereas six-membered ketal rings were obtained only in a few cases by condensing derivatives of polyhydric alcohols; no seven-membered ring formation has been reported so far.

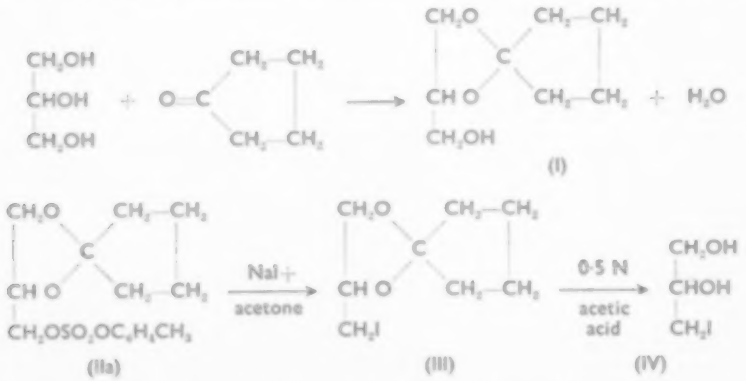
[5] H. S. Hills and H. Hibbert, *J. Amer. Chem. Soc.* **45**, 3122 (1923).
[6] R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.* **66**, 1909 (1944); A. T. Hess, R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.* **70**, 765 (1948).
[7] S. A. Barker and E. J. Bourne, *J. Chem. Soc.* 905 (1952).
[8] S. A. Barker, E. J. Bourne and D. H. Whiffen, *J. Chem. Soc.* 3865 (1952).
[9] H. C. Brown, R. S. Fletcher and J. Johansen, *J. Amer. Chem. Soc.* **73**, 212 (1951); H. C. Brown and M. Borkowski, *J. Amer. Chem. Soc.* **74**, 1894 (1952).
[10] H. C. Brown, J. H. Browster and H. Schlecher, *J. Amer. Chem. Soc.* **76**, 467 (1954).
[11] J. C. Irvine, J. L. A. Macdonald and Ch. W. Soutar, *J. Chem. Soc.* **107**, 337 (1915); H. Hibbert and J. Morazain, *Canad. J. Res.* **2**, 214 (1930); *Chem. Abstr.* **24**, 2988 (1930); N. M. Carter, *Ber. Dtsch. Chem. Ges.* **63B**, 2399 (1930); E. Baer and H. O. L. Fischer, *J. Amer. Chem. Soc.* **67**, 944 (1945).
[12] R. B. Tripson and L. H. Cretcher, *J. Org. Chem.* **8**, 95 (1943); R. Hann, A. T. Ness and C. S. Hudson, *J. Amer. Chem. Soc.* **66**, 73 (1944); E. Valentin and D. Tomkuljak, *Chem. Zvesti* **3**, 146 (1949), *Chem. Abstr.* **44**, 7234 (1950).
[13] H. H. Strain, *J. Amer. Chem. Soc.* **56**, 1756 (1954); B. C. Pressman, L. Andersen and H. A. Lardy, *J. Amer. Chem. Soc.* **72**, 2404 (1950); E. J. Bourne, G. P. McSweeney and M. Stacey, *J. Chem. Soc.* 1408 (1952).
[14] E. J. Bourne, G. P. McSweeney and L. F. Wiggins, *J. Chem. Soc.* 2542 (1952).
[15] E. Fischer and Ch. Rund, *Ber. Dtsch. Chem. Ges.* **49**, 88 (1916); L. F. Wiggins, *J. Chem. Soc.* 13 (1946).
[16] E. Fischer, *Ber. Dtsch. Chem. Ges.* **48**, 266 (1915); A. Pizzarello and W. Freudenberg, *J. Amer. Chem. Soc.* **61**, 611 (1939); R. Hann, W. Maclay and C. S. Hudson, *J. Amer. Chem. Soc.* **61**, 2432 (1939).

Ketones other than acetone have rarely been used. *cyclo*Hexanone is the only cyclic ketone which has been condensed, the other reactant being mannitol.[17]

In the present work the condensations of *cyclo*pentanone with glycol, glycerol, pentaerythritol, *meso*erythritol, arabitol, mannitol and sorbitol, as well as of *cyclo*hexanone with pentaerythritol and *meso*erythritol, are described. Condensations were carried out in the presence of gaseous hydrochloric acid, concentrated sulphuric acid and phosphorus pentoxide. Owing to the fact that polyhydroxy compounds are very sparingly soluble in cyclic ketones, 3–5 moles per mole of polyhydroxy compound were used and in some cases even a much greater excess.

Glycol has been condensed with *cyclo*pentanone under the experimental conditions given by Dworzak[3] for the condensation of glycol with acetone, i.e. in the presence of 40% suphuric acid and at elevated temperatures. Boeseken and Tellegan[18] have reported that they were unable to carry out the condensation of *cyclo*pentanone with glycol in the presence of either gaseous hydrochloric or concentrated sulphuric acid; but Salmi[3] by azeotropic elimination of the water formed in the course of the reaction, succeeded in obtaining the condensation product. The *cyclo*pentylideneglycol prepared in the present work was identical with that obtained by Salmi; the yield of the reaction was very small, probably owing to the self-condensation of *cyclo*pentanone.

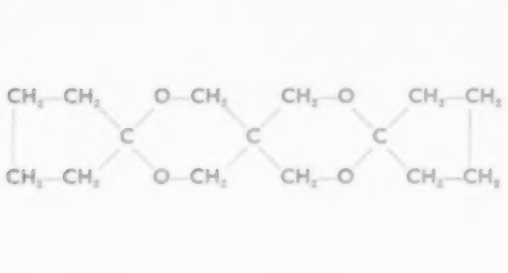
The condensation of glycerol with *cyclo*pentanone was carried out in the presence of gaseous hydrochloric acid and sodium sulphate as well as in the presence of concentrated sulphuric acid. The condensation product (I) was obtained in yields ranging from 41 to 51 per cent. The presence of one free hydroxy group in compound (I) was demonstrated by preparing the crystalline toluene-*p*-sulphonate (tosylate) (II) and mono-3:5-dinitrobenzoate. In order to establish whether compound (I) could be considered as a 1:2- or 1:3-glycerol derivative, the *p*-tosylate (II) was heated with sodium iodide in acetone at 100°. It has long been known, from the works of Oldham and Rutherford,[19] that the toluenesulphonate group could be displaced by iodine when attached to a primary carbon atom, whereas the same group on a secondary carbon atom is displaced only with difficulty. On heating the compound (II) with sodium iodide at 100°, either in a sealed tube or at atmospheric pressure, *cyclo*pentylidenemonoiodohydrin (III) was obtained. Hydrolysis of compound (III) with



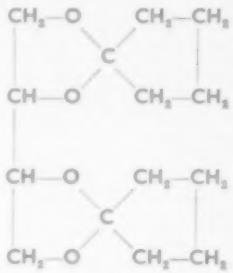
[17] E. J. Bourne, W. M. Corbett and D. Erilinne, *J. Chem. Soc.* 786 (1950).
[18] J. Boeseken and F. Tellegan, *Rec. Trav. Chim. Pays-Bas* **57**, 133 (1938).
[19] J. W. H. Oldham and J. K. Rutherford, *J. Amer. Chem. Soc.* **54**, 366 (1932).

0·5 N acetic acid afforded glyceroliodohydrin, identical with an authentic specimen prepared according to the method of Glattfeld and Klaas.[20]

The tetritols, pentaerythritol and *meso*erythritol were condensed with *cyclo*pentanone. The analyses of the products obtained have shown that in both cases all four hydroxy groups had reacted and that di*cyclo*pentylidene derivatives (V) and (VI) were obtained. It has been assumed that in the case of *meso*erythritol the adjacent hydroxy groups had been involved in the ketal formation and that the condensation product was 1:2–3:4-di*cyclo*pentylidene*meso*erythritol. (This assumption has been made in connexion with the determined structure of *cyclo*pentylideneglycerol.)



(V)



(VI)

The condensation of *cyclo*pentanone with L-arabitol yielded a syrupy product, which was identified by preparation of a crystalline toluene-*p*-sulphonate. According to the analysis of this derivative, di*cyclo*pentylidenearabitol was obtained.

The condensation with hexitols (D-mannitol and D-sorbitol) proceeded with the formation of the corresponding tri*cyclo*pentylidene derivatives, thus showing that all six hydroxy groups were involved in the reaction.

By condensing *cyclo*hexanone with pentaerythritol and *meso*erythritol, the corresponding di*cyclo*hexylidene derivatives were obtained.

All the condensation products were found to be crystalline solids (except those of glycol, glycerol and L-arabitol), soluble in common organic solvents but insoluble in water. The specific rotations of the compounds in question, owing to their cyclic structures, were much greater than those of the corresponding alcohols.

Condensations of monosaccharides with cyclo*pentanone and* cyclo*hexanone*

The published literature concerning the acetonisation of monosaccharides is rather complex, since most of the monosaccharides have been condensed with acetone. The most important references concern arabinose,[21] xylose,[22] mannose,[23] glucose,[24]

[20] J. W. E. Glattfeld and R. Klaas, *J. Amer. Chem. Soc.* **55**, 1117 (1933).

[21] E. Fischer, *Ber. Dtsch. Chem. Ges.* **28**, 1145 (1895); H. Ohle and G. Berend, *Dtsch. Ber. Chem. Ges.* **60**, 810 (1927).

[22] O. Svanberg, *Ber. Dtsch. Chem. Ges.* **56**, 863 (1923); K. Freudenberg and O. Svanberg, *Ber. Dtsch. Chem. Ges.* **55**, 3239 (1922); W. N. Haworth and Ch. R. Porter, *J. Chem. Soc.* 611 (1928).

[23] K. Freudenberg and R. Hixon, *Ber. Dtsch. Chem. Ges.* **56**, 2119 (1923); *Ibid.* **58**, 300 (1925); H. Ohle and G. Berend, *Ber. Dtsch. Chem. Ges.* **58**, 2590 (1925); J. Irvine and A. F. Skinner, *J. Chem. Soc.* 1089 (1926).

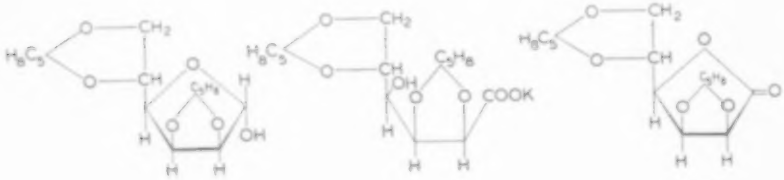
[24] J. Irvine and J. Patterson, *J. Chem. Soc.* **121**, 2146 (1922); J. Macdonald, *J. Chem. Soc.* **103**, 1896 (1913); J. Irvine and T. Hogg, *J. Chem. Soc.* **105**, 1386 (1914); K. Freudenberg and E. Doser, *Ber. Dtsch. Chem. Ges.* **56**, 1243 (1923); P. Karrer and O. Hurwitz, *Helv. Chim. Acta.* **4**, 728 (1921); C. G. Anderson, W. Charlton and W. N. Haworth, *J. Chem. Soc.* 1329 (1929).

galactose,[25] altrose,[26] gulose,[27] talose,[28] idose,[29] fructose,[30] sorbose,[31] tagatose[32] and psycose.[33] The structures of the condensation products have been determined beyond question only in a few cases; usually, among many possible structures the most probable were suggested as being correct.

Among cyclic ketones only *cyclo*hexanone has been condensed with glucose.[34]

By condensing the pentoses D-xylose and L-arabinose with *cyclo*pentanone and *cyclo*hexanone in the presence of concentrated sulphuric acid the corresponding di-derivatives have been obtained. The condensation products were shown to be optically active crystalline solids (contrary to diacetonexylose, which is a liquid) that do not reduce Fehling's solution and are insoluble in water but soluble in most organic solvents. *cyclo*Hexanone was found to condense much more readily than *cyclo*pentanone.

The condensations of D-giucose and D-mannose with *cyclo*pentanone and *cyclo*hexanone resulted in the formation of the corresponding di-derivatives. The condensation product of *cyclo*pentanone with D-glucose was obtained after a long series of experiments, the yield being very poor (0·25 per cent). The condensation of the same ketone with D-mannose proceeded much more readily, the yields being quite satisfactory (44 per cent). The products obtained were likewise solids having no reducing properties. According to published data, mannose reacts with acetone in the furanoside form. In order to find out whether in the condensations with *cyclo*pentanone and *cyclo*hexanone mannose reacted in the same furanoside form, di*cyclo*pentylidenemannose (VII) was subjected to oxidation with potassium permanganate in alkaline solution to yield the potassium salt of the corresponding mannonic acid (VIII). By addition of one equivalent of 0·5 N sulphuric acid the lactone of di*cyclo*pentylidenemannonic acid (IX) was obtained. This oxidation confirms the presence of a free aldehyde group in compound (VII), whereas the easy formation of the



VII VIII IX

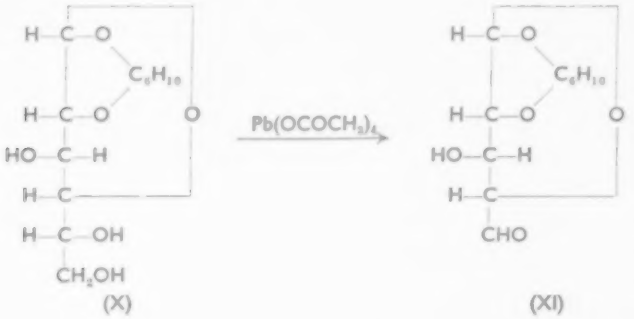
[25] H. Ohle and G. Berend, *Ber. Dtsch. Chem. Ges.* **58,** 2585 (1925).
[26] M. Steibner and T. Reichstein, *Helv. Chim. Acta* **19,** 1011 (1936); F. H. Newth and L. F. Wiggins, *J. Chem. Soc.* 1734 (1950).
[27] K. Iwadare, *Bull. Chem. Soc. Japan* **18,** 226 (1943).
[28] W. Bossard, *Helv. Chim. Acta* **18,** 482 (1935).
[29] K. Iwadare, *Bull. Chem. Soc. Japan.* **19,** 27 (1944).
[30] J. Irvine and A. Hydn, *J. Chem. Soc.* **95,** 1220 (1909); J. Irvine and J. P. Scott, *J. Chem. Soc.* **103,** 564 (1913); W. N. Haworth, E. L. Hirst and A. Learner, *J. Chem. Soc.* 1040 (1927); C. G. Anderson, W. Charlton and W. N. Haworth, *J. Chem. Soc.* 1337 (1929); H. Ohle and G. Berend, *Ber. Dtsch. Chem. Ges.* **60,** 1159 (1927); W. L. Wolfrom, W. L. Shiling and W. W. Binkley, *J. Amer. Chem. Soc.* **72,** 4544 (1950).
[31] T. Reichstein and O. Grüssner, *Helv. Chim. Acta* **17,** 311 (1934); H. Ohle, *Ber. Dtsch. Chem. Ges.* **71B,** 762 (1938).
[32] L. D. Bruyn and W. A. van Ekenstein, *Rec. Trav. Chim. Pays-Bas* **16,** 265 (1897); T. Reichstein and J. Bossard, *Helv. Chim. Acta* **17,** 753 (1934).
[33] M. Steigner and T. Reichstein, *Helv. Chim. Acta* **18,** 790 (1935).

lactone ring speaks in favour of the furanoside structure of the mannose being involved in the reaction.

Di*cyclo*pentylidene-D-mannose is *dextro*rotatory, the potassium salt of the di*cyclo*-pentylidene-D-mannonic acid (VIII) is *laevo*rotatory and the lactone (IX), in accordance with Hudson's lactone rule, is again *dextro*rotatory.

The condensation of D-mannose with *cyclo*hexanone resulted in the formation of a crystalline di-derivative.

The structure of di*cyclo*hexylidene-D-glucose has been determined by Hockett *et al.*[34] According to their work, the condensation product was found to be the 1:2-5:6-derivative of the glucofuranose. In an attempt to prove directly the size of the lactol ring, mono*cyclo*hexylidene-D-glucose, obtained by hydrolysis of the di-derivative, was oxidised with lead tetra-acetate. The crystalline derivative obtained was 1:2-mono*cyclo*hexylidene-trihydroxyglutar-dialdehyde (XI), which was identified by conversion to its monosemicarbazone (the second aldehyde group being blocked by the *cyclo*hexylidene). The formation of this product is only possible if the starting substance has a furanoside structure.



(X) (XI)

The condensation of D-fructose with *cyclo*pentanone produced a syrupy product, which was characterised by preparation of its toluene-*p*-sulphonate. The condensation of the same ketose with *cyclo*hexanone gave likewise a di-derivative, but in crystalline form. Since the analyses of the products obtained corresponded to the di-derivatives and attempts to oxidise the product with potassium permanganate failed, it has been assumed that the most probable structure of the derivative concerned is (XII). In the case of the alternative structure (XIII), upon oxidation the potassium salt of *cyclo*pentylidene-2-oxogluconic acid would have been obtained.

XII XIII

[34] R. C. Hockett, R. E. Miller and A. Scattergood, *J. Amer. Chem. Soc.* **71**, 3072 (1949).

EXPERIMENTAL

cyclo*Pentylideneglycol.* In a round-bottomed flask fitted with a mechanical stirrer and a reflux condenser there were placed glycerol (31 g), *cyclo*pentanone (42 g) and 4 drops of 40% sulphuric acid. The reaction mixture was stirred and heated on a water bath for 10 hr, cooled and extracted with ether, and the ethereal solution was dried and distilled. The fraction boiling from 136 to 155° was collected and treated with twice its volume of saturated bisulphite solution to remove the unchanged *cyclo*pentanone. The filtrate was extracted with ether and the ethereal solution was dried and distilled. The fraction boiling at 153° was collected (4 g, 6·2 per cent), $n_D^{20.5°}$ 1·4537, $d_4^{20.5°}$ 1·024 (M.R. found: 33·82; $C_7H_{12}O_2$ requires: 33·47).

cyclo*Pentylideneglycerol* (I). A mixture of glycerol (20 g), gaseous hydrochloric acid (0·4 g) and anhydrous sodium sulphate (8 g) was stirred for 24 hr at room temperature. After neutralisation, the inorganic salts were removed by filtration and, after addition of a small amount of silver oxide, the filtrate was distilled under diminished pressure. The unchanged *cyclo*pentanone having been removed, the fraction distilling at 127–129°/10 mm was collected (14 g, 41 per cent).

Glycerol (10 g), *cyclo*pentanone (20 g) and 95% sulphuric acid (3 g) were kept at room temperature for 24 hr and occasionally shaken. The reaction mixture was made neutral with lead carbonate, filtered and distilled; b.p. 122–123°/16 mm (9·3 g, 54 per cent), n_D^{20} 1·4793, d_4^{18} 1·073 (M.R. found 39·30. $C_8H_{14}O_3$ requires: 39·63. Found: C, 60·50; H, 8·84. $C_8H_{14}O_6$ requires C, 60·75; H, 8·86 per cent).

cyclo*Pentylideneglycerol* 3:5-*dinitrobenzoate*. 3:5-Dinitrobenzoyl chloride (1·2 g) and *cyclo*pentylideneglycerol (1 g) were dissolved in anhydrous benzene. To the clear solution pyridine (2 ml, dried and distilled over potassium hydroxide) was added. After standing for 1 hr the reaction mixture was diluted with dry ether; pyridine hydrochloride separated and was collected, and the ethereal solution was washed successively with 2% sodium hydroxide, 2% hydrochloric acid and water and then dried and the ether was finally evaporated. The yield was 1·5 g (68 per cent), m.p. 79° after recrystallisation from ethanol (Found:C, 51·18; H, 4·72; N, 8·40. $C_{15}H_{16}O_8N_2$ requires: C, 51·13; H, 4·54; N, 7·95 per cent).

cyclo*Pentylideneglycerol toluene*-p-*sulphonate* (II). Toluene-*p*-sulphonyl chloride (15 g), dissolved in anhydrous pyridine (30 ml), was added to a solution of *cyclo*-pentylideneglycerol (10 g) in dry pyridine (10 ml). The reaction mixture was kept in an ice-bath for some time and then at room temperature for 36 hr. The pyridine hydrochloride that separated was dissolved by adding a small quantity of water, and the mixture was poured with stirring into ice-water (150 g). The heavy oil was extracted with chloroform and the chloroform solution was separated, washed, dried and evaporated to a thick syrup, which was triturated with light petroleum. The solid so obtained (7 g, 35 per cent) was collected and crystallised from light petroleum and ethanol, m.p. 38° (Found: S, 10·08; $C_{15}H_{20}O_5S$ requires: S, 10·25 per cent).

cyclo*Pentylideneglycerolmonoiodohydrin* (III). A mixture of compound (II) (3 g) and sodium iodide (3·7 g) was dissolved in anhydrous acetone and heated in a sealed tube at 100° for 12 hr. The sodium toluene-*p*-sulphonate was collected and the acetone was evaporated to leave a reddish brown syrup, which decomposed when subjected to a distillation under diminished pressure.

Compound (II) (9 g) and sodium iodide (11 g) were dissolved in dry acetone and heated on an oil-bath for 20 hr. The yield of sodium toluene-*p*-sulphonate was 4 g

(73 per cent). After evaporation of the acetone, the syrupy residue was treated first with light petroleum to remove compound (II) and then with ether to remove the unchanged sodium iodide. The filtrate yielded on evaporation a syrupy product (6 g, 78 per cent) that contained iodine and did not solidify at temperatures as low as −21°.

Glycerolmonoiodohydrin (IV). An emulsion of compound (III) (6 g) in water (18 ml) and 5 N hydrochloric acid (2 drops) was heated under reflux until a clear solution was obtained. The cold solution was made neutral to litmus and extracted with ether. After evaporation of the ether, an oily product was obtained, which, when triturated with light petroleum, gave a crystalline solid. After recrystallisation from chloroform–light petroleum it had m.p. 48°.[20]

*Di*cyclo*pentylidenepentaerythritol* (V). A mixture of pentaerythritol (3 g), *cyclo*pentanone (11·6 g) and concentrated sulphuric acid (5 drops) was stirred for 3 days. Then potassium hydroxide was added until the reaction mixture was alkaline and the separated product was collected and washed thoroughly with water. The yield was 2·3 g (24 per cent), having after recrystallisation from ethanol m.p. 152° (Found: C, 67·08; H, 9·17. $C_{15}H_{24}O_4$ requires: C, 67·16; H, 8·95 per cent).

*Di*cyclo*hexylidenepentaerythritol.* A mixture of pentaerythritol (6 g) *cyclo*hexanone (25 g) and concentrated sulphuric acid (5 drops) was stirred for 1 day. When all the pentaerythritol had dissolved, the mixture was neutralised and poured into a large volume of water. The solid that separated (10 g, 87 per cent) was collected and recrystallised from ethanol, m.p. 135° (Found: C, 68·96; H, 9·54. $C_{17}H_{28}O_4$ requires: C, 68·91; H, 9·45 per cent).

*Di*cyclo*pentylidene*meso*erythritol*(VI). This was prepared in the same way as the pentaerythritol derivative (V). After being recrystallised from 60% ethanol it had m.p. 64°; yield was 40 per cent (Found: C, 66·16; H, 8·84. $C_{14}H_{22}O_4$ requires: C, 66·14; H, 8·66 per cent).

*Di*cyclo*hexylidene*meso*erythritol.* This was prepared in the same way as the *cyclo*pentylidene derivative (VI). The yield was 87 per cent. After being recrystallised from ethanol m.p. 95 °(Found: 67·86; 9·35. $C_{16}H_{26}O_4$ requires: C, 68·08; H, 9·21 per cent).

*Di*cyclo*pentylidene*-L-*arabitol.* A mixture of arabitol (1·5 g, obtained by the reduction of L-arabinose with Raney nickel[35]), *cyclo*pentanone (7 g) and concentrated sulphuric acid (0·25 ml) was stirred for 1 day at room temperature. The reaction mixture was made neutral and extracted with ether. The etheral solution was washed with water and after evaporation of the ether yielded a syrupy product (0·8 g, 28 per cent), insoluble in water.

cyclo*Pentylidene*-L-*arabitol toluene*-p-*sulphonate.* This was prepared in the same way as compound (II). Yield 32 per cent. Recrystallised from light petroleum, it had m.p. 68° (Found: S, 7·30; $C_{22}H_{33}O_7S$ requires S, 7·30 per cent).

*Tri*cyclo*pentylidene*-D-*mannitol.* Phosphorus pentoxide (5 g) was added to a stirred mixture of mannitol (9 g) and *cyclo*pentanone (50 ml). The reaction mixture was stirred for some hours, and then made neutral and poured into water. The oily product that separated turned into a crystalline mass on standing. The yield was 4·5 g (25 per cent). Recrystallised from ethanol, it had m.p. 70°, $[\alpha]_D^{18}$ +11·27° (*c*, 1·35 in

[35] K. Gätzi and T. Reichstein, *Helv. Chim. Acta* **21**, 195 (1938).

chloroform) (Found: C, 66·23; H, 8·35. $C_{21}H_{32}O_6$ requires: C, 66·31; H, 8·42 per cent).

*Tri*cyclo*pentylidene*-D-*sorbitol*. This was prepared in the same way as the mannitol derivative from D-sorbitol (2 g), *cyclo*pentanone (8 ml) and concentrated sulphuric acid. After being recrystallised from ethanol, it had m.p. 75° $[\alpha]_D^{18}$ +7·3° (*c*, 1·09 in ethanol) (Found: C, 66·51; H, 8·67. $C_{21}H_{32}O_6$ requires: C, 66·31; H, 8·42 per cent).

*Di*cyclo*pentylidene*-L-*arabinose*. L-Arabinose (2 g), *cyclo*pentanone (20 g) and concentrated sulphuric acid (15 drops) were stirred for 24 hr. Since only a small amount of the sugar was dissolved, the reaction mixture was filtered (when 1·5 g of arabinose was recovered), and the filtrate was made neutral, and then diluted with water and extracted with ether. After evaporation of the ether a solid product was obtained (0·5 g), 53 per cent. After being recrystallised from 60% ethanol, it had m.p. 62° (Found: C, 64·60; H, 8·12. $C_{15}H_{22}O_5$ requires: C, 63·82; H, 7.80 per cent).

*Di*cyclo*hexylidene*-L-*arabinose*. This was prepared in the same way as the *cyclo*pentylidene derivative from L-arabinose (4 g), *cyclo*hexanone (25 g) and concentrated sulphuric acid (0·7 ml). The yield was 73 per cent; after being recrystallised from 70% ethanol, it had m.p. 86° (Found: C, 65·78; H, 8·35. $C_{17}H_{26}O_5$ requires: C, 65·80; H, 8·38 per cent).

*Di*cyclo*pentylidene*-D-*xylose*. A suspension of D-xylose (1 g), *cyclo*pentanone (20 g) and concentrated sulphuric acid was stirred for 48 hr and then neutralised. The oil thus obtained was dissolved in ethanol and, on adding water, a crystalline solid was precipitated (0·6 g, 31 per cent). Recrystallised from 50% ethanol, it had m.p. 89° (Found: C, 63·45; H, 7·70. $C_{15}H_{22}O_5$ requires: C, 63·82; H, 7·80 per cent).

*Di*cyclo*hexylidene*-D-*xylose*. This was prepared from D-xylose (2 g), *cyclo*hexanone (20 g) and concentrated sulphuric acid (15 drops). The yield was 3 g (72 per cent). After recrystallisation from 80% ethanol it had m.p. 104° (Found: C, 65·88; H, 8·49. $C_{17}H_{26}O_5$ requires: C, 65·80; H, 8·38 per cent).

*Di*cyclo*pentylidene*-D-*mannose* (VII). This was obtained by condensing D-mannose (2 g) with *cyclo*pentanone in the presence of concentrated sulphuric acid. The yield was 1·5 g (44 per cent). After being recrystallised from 40% ethanol, it had m.p. 116°, $[\alpha]_D^{18}$ +8·7° (*c*, 1·04 in alchol) (Found: C, 61·81; H, 7·90. $C_{16}H_{24}O_6$ requires: C, 61·53; H, 7·69 per cent).

*Di*cyclo*hexylidene*-D-*mannose*. This was prepared in the same way as the *cyclo*pentylidene derivative. The yield was 52 per cent, m.p. 122° (Found: C, 63·72; H, 8·00. $C_{18}H_{28}O_6$ requires: C, 63·52; H, 8·23 per cent).

Potassium salt of cyclo*pentylidene*-D-*mannonic acid* (VIII). Potassium permanganate (0·33 g) was added to a suspension of compound (VII) (1 g) in aqueous potassium hydroxide (0·18 g in 10 ml of water). The reaction mixture was stirred and heated for 6 hr, and then filtered, and the filtrate was evaporated under diminished pressure. The potassium salt was treated with acetone to remove the starting material; the product had m.p. 235° (dec.), $[\alpha]_D^{18}$ −23·9° (*c*, 2·55 in water).

*Lactone of di*cyclo*pentylidene*-D-*mannonic acid* (IX). To a solution of compound (VIII) in a small amount of water the equivalent amount of 0·5 N sulphuric acid was added and the resulting solution was extracted with ether. From the ethereal solution, on evaporation, a crystalline solid was obtained, m.p. 129°, $[\alpha]_D^{18}$ +35·98° (*c*, 1·32 in chloroform) (Found: C, 62·03; H, 7·17. $C_{16}H_{22}O_6$ requires: C, 61·93; H, 7·09 per cent).

Dicyclopentylidene-D-glucose. A mixture of zinc chloride (6 g), phosphorus pentoxide (1 g) and 85% phosphoric acid (2 g) was added to a stirred suspension of D-glucose (5 g) in *cyclo*pentanone (100 ml). The reaction mixture was stirred for 24 hr, and then neutralised with potassium carbonate. The inorganic salts and the unchanged glucose were removed by filtration and washed with ether; the dark brown filtrate was made neutral with some more potassium carbonate. The excess of *cyclo*pentanone was removed by distillation under diminished pressure and the oil thus obtained, when treated with ethanol and light petroleum, turned on standing into a crystalline mass (0·2 g, 2·5 per cent). After being recrystallised from light petroleum and ethanol, it had m.p. 104° (Found: C, 61·72; H, 7·78. $C_{16}H_{24}O_6$ requires: C, 61·53; H, 7·69 per cent).

Dicyclohexylidene- and moncyclohexylidene-D-glucose (X). These were prepared according to the procedures given by Hockett *et al.*[34]

1:2-*Monocyclohexylidene*-xylo*trioxyglutarialdehyde* (XI). To a stirred solution of lead tetra-acetate (13·4 g) in dry benzene, heated under reflux, there was added dropwise mono*cyclo*hexylidene-D-glucose (8 g), dissolved in dry benzene (200 ml). After the addition, the reaction mixture was heated on a water bath for ½ hr, lead acetate being thereby precipitated. The mixture was then filtered and the filtrate was evaporated. The oily residue was triturated with water and the solid so obtained (5 g, 71 per cent) was recrystallised from 50% ethanol, m.p. 178° (Found: C, 58·06; H, 7·23. $C_{11}H_{16}O_5$ requires: C, 57·89; H, 7·01 per cent).

Semicarbazone of compound (XI). Compound (IX) (1 g), dissolved in ethanol (20 ml) was added to a solution of sodium acetate (3 g) and semicarbazide hydrochloride (2 g) in water (16 ml). The reaction mixture was heated under reflux for ½ hr; on cooling, crystals of the semicarbazone separated (1 g, 80 per cent), m.p. 215° (dec.) (Found: C, 50·63; H, 6·92; N, 14·55. $C_{12}H_{19}O_5N_3$ requires: C, 50·52; H, 6·68; N, 14·37 per cent).

Dicyclopentylidene-D-fructose (XII). A mixture of D-fructose (2 g), *cyclo*pentanone (25 g) and concentrated sulphuric acid (1 ml) was stirred at room temperature for 40 hr. The reaction mixture was neutralised and then poured into water and extracted with ether. On evaporation of the ethereal solution, a syrupy residue was obtained (2 g, 58 per cent).

Dicyclopentylidene-D-fructose toluene-p-sulphonate. This was prepared in the same way as compound (II) from compound (XII) (2 g) and toluene-*p*-sulphonyl chloride (1·5 g). The yield was 1·5 g (50 per cent). After being recrystallised from 50% ethanol, it had m.p. 116° (Found: S, 6·77. $C_{23}H_{30}O_8S$ requires: S, 6·88 per cent).

Dicyclohexylidene-D-fructose. A mixture of D-fructose (2 g), *cyclo*hexanone (10 g) and concentrated sulphuric acid was stirred at room temperature. After a short period all the starting material had dissolved and the condensation product was separated. The reaction mixture was then made alkaline and poured into water; an oily product separated, and when treated with light petroleum, it formed a crystalline mass (2·3 g, 62 per cent); after recrystallisation from 50% ethanol it had m.p. 142° (Found: C, 63·78; H, 8·27. $C_{18}H_{28}O_6$ requires: C, 63·52; H, 8·23 per cent).

SUMMARY

Polyhydroxy compounds and monosaccharides were found to react with *cyclo*pentanone and *cyclo*hexanone to yield mono-, di- and tri-*cyclo*pentylidene and -*cyclo*hexylidene derivatives, respectively.

1. By condensing *cyclo*pentanone and *cyclo*hexanone with polyhydric alcohols, the following condensation products were obtained: *cyclo*pentylideneglycerol, di*cyclo*pentylidene-pentaerythtritol, -*meso*erythritol and -L-arabitol, tri*cyclo*pentylidene-D-sorbitol and -D-mannitol, as well as di*cyclo*hexylidene-pentaerythritol and -*meso*erythritol.

2. By condensing *cyclo*pentanone and *cyclo*hexanone with monosaccharides, the following compounds were obtained: di*cyclo*pentylidene-D-xylose, -L-arabinose, -D-glucose, -D-mannose and -D-fructose, as well as di*cyclo*hexylidene-D-xylose, -L-arabinose, -D-mannose and -D-fructose.

3. The structure of *cyclo*pentylideneglycerol has been established by conversion into its toluene-*p*-sulphonyl derivative, which, on treatment with sodium iodide in acetone at 100°C yielded the known glycerolmonoiodohydrin.

4. The structure of di*cyclo*pentylidene-D-mannose has been established by converting it into the lactone of di*cyclo*pentylidene-D-mannonic acid.

5. The furanoside structure of di*cyclo*hexylidene-D-glucose has been confirmed by oxidation with lead terra-acetate; the resulting mono*cyclo*hexylidene-D-*xylo*-trihydroxygutardialdehyde was characterised by conversion into its semicarbazone.

6. In the condensation reactions with polyhydroxy compounds *cyclo*pentanone and *cyclo*hexanone behave similarly to acetone—the resulting condensation products having five-membered ring structures.

7. In the course of the condensations *cyclo*hexanone reacted much more readily than *cyclo*pentanone, this fact being consistent with the proposed I-strain hypothesis.

8. Unlike diacetonexylose, *cyclo*pentylidene- and *cyclo*hexylidene-xylose are crystalline solids that can be easily isolated and purified.

Tetrahedron, 1958, Vol. 4, pp. 197–200. Pergamon Press Ltd., London

NOTES

Esters containing phosphorus—XVI*

A new colour reaction for the detection and estimation of dialkyl phosphites

(*Received* 26 *June* 1958)

THE formation of a colour on treatment of a solution of *m*-dinitrobenzene in acetone with alkali was first observed by Janovsky.[1] This reaction has been extended by several workers[2,3,4] to a wide range of aromatic nitro-compounds and of compounds containing the >CH—CO— grouping, and has many uses both as a qualitative test[5] and for the quantitative analysis of, for instance, aromatic nitro-compounds,[6] creatinine,[7] digitoxin[8] and various carbonyl compounds.[9] During the course of our investigations into certain aspects of the chemistry of peroxidase and of phosphorous esters,[10] we have recently observed that acetone can be replaced by one of several dialkyl phosphites, when a blue or purple colour is usually obtained. This affords a further illustration of the similarity of dialkyl phosphites to carbonyl compounds, demonstrated for example in recent years by the many instances of base-catalysed addition of phosphites to carbonyl functions, a reaction formally analogous to the aldol condensation.

Further investigation has shown us that the colours are produced most rapidly with dialkyl phosphites in aqueous sodium hydroxide, but that they then become brown and soon fade. It has been found convenient to carry out the reaction in a saturated solution of sodium bicarbonate, when dialkyl phosphites give fairly stable colours, in contrast to acetone and similar compounds, which give little or no coloration under these conditions. A representative selection of dialkyl phosphites ($[RO]_2POH$, R = methyl, ethyl, *iso*propyl, *tert.*-butyl, benzyl, *cyclo*hexyl, 1-ethylpropyl, 1-carbethoxyethyl, 3-methylbutyl or 1:3-dimethylbutyl) has been examined; all have given positive reactions. A wide variety of substituted *m*-dinitrobenzenes may be used, but the reagent of choice is 3:5-dinitrobenzoic acid, which has the advantage of solubility in aqueous media and the property of intense colour formation. The test is sensitive to a phosphite concentration of 1 : 10,000.

Most other classes of organo-phosphorus compounds do not give this reaction, but substances (such as diethyl α-hydroxyethylphosphonate, diethyl phosphorochloridite, and tetraethyl pyrophosphite), which readily undergo cleavage to dialkyl phosphites on treatment with alkali, can be detected. Diethyl phosphorocyanidate gives a brown solution similar to that produced by the action of inorganic cyanide on 3:5-dinitrobenzoic acid. The reaction is also given by a number of compounds (*cyclo*pentadiene, pyrrole, nitromethane, etc.) which form anions under alkaline conditions, but the colorations are usually quite unlike the blue or purple hues formed by phosphites.

The reaction can be used for the quantitative determination of dialkyl phosphites by a colorimetric method. The following procedure combines simplicity of apparatus and operation with reasonable accuracy. The sample of phosphite (1 mg or more) is diluted with water to 1·0 ml, and

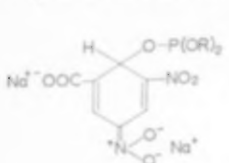
* Paper XV. B. B. Hunt and B. C. Saunders, *J. Chem. Soc.* 2413 (1957).

[1] J. V. Janovsky and L. Erb, *Ber. Dtsch. Chem. Ges.* **19**, 2155 (1886).
[2] M. J. Newlands and F. Wild, *J. Chem. Soc.* 3686 (1956).
[3] F. Reitzenstein and G. Stamm, *J. prakt. Chem.* **81**, 167 (1910).
[4] T. Canbäck, *Farm. Revy* **48**, 217, 234, 249 (1949).
[5] F. G. Mann and B. C. Saunders, *Practical Organic Chemistry* (3rd Ed.) pp. 216, 261, 293. Longmans, Green, London (1952).
[6] F. L. English, *Analyt. Chem.* **20**, 745 (1948).
[7] J. J. Carr, *Analyt. Chem.* **25**, 1859 (1953).
[8] T. Canbäck, *Svensk Farm. Tid.* **51**, 261 (1947).
[9] T. Canbäck, *Farm. Revy* **46**, 802 (1947).
[10] B. C. Saunders and B. P. Stark, *Tetrahedron* **4**, 169 (1958).

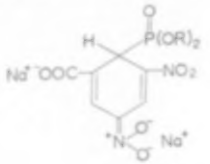
a solution of 3:5-dinitrobenzoic acid (0·5 gm) in saturated aqueous sodium bicarbonate (10 ml) is added with shaking. After a suitable interval (40 min–3 hr) the solution is compared in a visual colorimeter with a standard solution containing an arbitrary amount of phosphite. The amount of phosphite present in the sample is obtained by comparison of the colorimeter reading with a calibration curve of readings from tubes containing known amounts of phosphite, measured against the same standard after the same time. Modifications may sometimes be necessary for individual phosphites.

The coloration of dialkyl phosphites with 3:5-dinitrobenzoic acid in the presence of alkali is not due to hydrolysis products (e.g. monoalkyl phosphite) since sodium monobenzyl phosphite fails to respond to the test, whereas diphenylphosphinous acid (Ph_2POH, which is incapable of undergoing hydrolysis) gives a positive reaction.

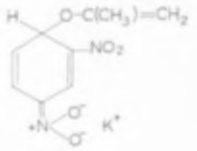
The nature of the coloured compounds formed by dialkyl phosphites is not yet clear. Since the reaction can be carried out in the presence of only traces of water if a strong organic base be substituted for alkali, it seems possible that compounds of the types (I) or (II) may be present, analogous to the quinonoid adducts (III) described by Gitis[11] in his work on the reaction with acetone.



(I)



(II)



(III)

A reaction rather similar to the Janovsky test is that in which sodium iodide is added to a solution of an aromatic nitro-compound in acetone or certain other solvents.[12] We have now found that in this test also, acetone can be replaced by a dialkyl phosphite; the colours obtained are similar to those produced in the presence of acetone. As in the case of acetone, the colours are bleached by the addition of water; free iodine is apparently not present.

Finally it may be mentioned that addition of dilute alkali to a mixture of a dialkyl phosphite and aqueous sodium nitroprusside gives generally a red or orange colour. Similar colours are given by acetone and related compounds.[4]

Further investigations into the mechanism, specificity and uses of these reactions are proceeding.

One of us (B. P. S.) is grateful to the D.S.I.R. for a Maintenance Grant.

University Chemical Laboratory
Lensfield Road
Cambridge, England

B. C. Saunders
B. P. Stark

[11] S. S. Gitis, *Zh. obshch khim.* **27**, 1894 (1957).
[12] R. W. Shellman, *J. Org. Chem.* **22**, 818 (1957).

Esters containing phosphorus—XVII*

Detection and estimation of dialkyl phosphites in the presence of trialkyl phosphites

(*Received* 15 *August* 1958)

We have recently recorded[1] that dialkyl phosphites and certain related compounds produce intense purple colours with alkaline solutions of 3:5-dinitrobenzoic acid.† Most trialkyl phosphites also give colours, probably because they undergo some dealkylation under these conditions. It has been

* Paper XVI: B. C. Saunders and B. P. Stark, *Tetrahedron* **4**, 197 (1958).

† It is considered convenient to designate the reaction involving colorations with 3:5-dinitrobenzoic acid under alkaline conditions as the 3:5-DB test.

[1] B. C. Saunders and B. P. Stark, *Tetrahedron* In press (1958).

found possible, however, to devise a method for the estimation of dialkyl and trialkyl phosphites in the presence of one another. The basis of this method is that the trialkyl esters react quantitatively with iodine to form dialkyl phosphoroiodidates (which do not respond to the 3:5-DB test), whereas the dialkyl esters do not react appreciably.[2] Thus, a rough estimation of the amount of trialkyl phosphite present can be obtained by titration with iodine. Addition of alkaline 3:5-dinitrobenzoate to the mixture thus obtained then permits colorimetric determination of the dialkyl phosphite. The method given below has been found suitable with mixtures of triethyl and diethyl phosphites, and is clearly capable of extension to other esters.

During our survey of the applicability of the 3:5-DB test to a wide range of compounds of different types, we have observed that a few inorganic anions give marked colours with 3:5-dinitrobenzoic acid. In 10 per cent sodium hydroxide solution, the most pronounced colours are those given by cyanide (red-brown, stable to acids), arsenite (red, unstable to acids), and sulphite (red, unstable to acids). Inorganic sulphides, persulphates, dithionites, and iodides, which give less distinct colours, interfere. Most other inorganic anions have negative reactions. Thiosulphates do not respond to the test, except after preliminary treatment with mineral acid (to liberate the sulphite) and then with alkali. Arsenite and sulphite can be distinguished by virtue of the fact that the latter, but not the former, gives a pink or red colour with 3:5-dinitrobenzoic acid in aqueous sodium bicarbonate solution, or in aqueous ammonia–ammonium sulphate solution (cf. Rothera's test for acetoacetate).[3] It is worthy of note that Feigl[4] has used potassium cyanide in acidic solution as a reagent for the detection of *m*-dinitro-compounds.

As an illustration of the use of this reaction with inorganic anions, we present a colorimetric method for the estimation of inorganic arsenite, and a method for the detection of arsenite on paper chromatograms.

The 3:5-DB test with inorganic ions may be summarised as follows. Preliminary work shows that the test may be of some use in the detection of cyanide, arsenite, and sulphite (see Table 1).

TABLE 1

Anion	3:5-dinitrobenzoic acid in 10% NaOH	3:5-DB test in $NH_3/(NH_4)_2SO_4$
Cyanide	Red-brown, stable to mineral acids.	Red–brown
Sulphite	Red, becoming faint yellow on addition of mineral acid.	Pink
Arsenite	Red, becoming weak yellow on addition of mineral acid.	No colour
Sulphide	Deep red, soon succeeded by brown and then yellow colour, with yellow precipitate. Bleached by acids, with evolution of H_2S.	brown–yellow
Persulphate	Slightly yellower than control test. Yellow in acid.	Very faint yellow
Dithionite	Yellower than control; yellow precipitate. Faint yellow in acid.	Pink
Iodide	Slightly more yellow than control; weak yellow in acid.	Weak yellow
Most other anions tested	No change in alkali.	No change.

[2] H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.* 921 (1945).
[3] A. C. H. Rothera, *J. Physiol.* 37, 491 (1908).
[4] F. Feigl, *Spot Tests* Vol. II, p. 125. Elsevier (1954).

EXPERIMENTAL

Estimation of diethyl phosphite in the presence of triethyl phosphite

The mixture is dissolved in ether (2 ml), and the solution cooled to 0°; a solution of iodine (10% in ether) is now added until a faint yellow colour persists. The volume of iodine solution added is noted. The mixture is shaken at room temperature for 45 min with a solution of 3:5-dinitrobenzoic acid (0·5 g) in saturated aqueous sodium bicarbonate solution (10 ml). 5 ml of the aqueous layer are then diluted to 20 ml, the diluted solution left for a further 10 min, and then compared with an arbitrary standard as previously described.[1] The colorimeter reading is compared with a calibration curve as before,[1] to give the concentration of diethyl phosphite.

Colorimetric estimation of inorganic arsenite

The procedure necessary is essentially the same as that previously described for dialkyl phosphites,[1] except that the 3:5-dinitrobenzoic acid should be dissolved in 10 per cent sodium hydroxide solution rather than in sodium bicarbonate. The method is suitable for the estimation of 10 mg or more of sodium arsenite; the dilution limit is ca. 1:200.

Detection of inorganic arsenites on paper chromatograms

The arsenite (ca. 50–100 μg) is applied to Whatman No. 1 filter paper, and an ascending chromatogram run overnight, with butan-1-ol saturated with 20 per cent aqueous acetic acid as solvent.[2] The paper is then dried and sprayed with a 5 per cent solution of 3:5-dinitrobenzoic acid in 10 per cent aqueous sodium hydroxide solution. Red spots (R_F 0·43) appear after a few minutes at room temperature, or more rapidly on warming.

Acknowledgement—Our thanks are due to the Department of Scientific and Industrial Research, for a maintenance grant to one of us (B. P. S.).

B. C. Saunders
B. P. Stark

University Chemical Laboratory
Lensfield Road
Cambridge, England

[2] M. Lederer, Unpublished experiments, quoted in E. Lederer and M. Lederer, *Chromatography* p. 339. Elsevier (1953).

Tetrahedron, 1958, Vol. 4, pp. 201–202. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATION

Transformation of steroids by Pseudomonas

(*Received* 20 *May* 1958)

DESPITE extensive studies on the transformations of steroids by a wide variety of micro-organisms, little has been described on the steroid transformations by *Pseudomonas* species. There are several interesting transformations of steroids by *Pseudomonas*, and in this communication the conversions of 4-pregnene-17α,21-diol-3,20-dione (I, Reichstein's Substance S) to 1,4-pregnadiene-17α,20β,21-triol-3-one (II) and 4-pregnene-11β,17α,21-triol-3,20-dione (III, hydrocortisone) by *Pseudomonas* sp. 109*, to II and 1,4-pregnadiene-17α,21-diol-3,20-dione (IV) by *Pseudomonas* sp. 125*, and to 4-pregnene-17α,20β,21-triol-3-one (V) by *Pseudomonas* sp. M8* are reported.

Pseudomonas sp. 109: This organism was isolated from soil and identified as closely akin to *Pseudomonas boreopolis*.[1] Incubation of I was carried out with a 24 hr culture of this organism at 30° for 17 hr in the synthetic medium which was employed in the study of pyoluteorin.[2] Extraction of the culture filtrate with ethyl acetate, followed by acetylation with acetic anhydride and pyridine afforded 20β,21-diacetoxy-1,4-pregnadiene-17α-ol-3-one (the 20,21-diacetate of II), m.p. 178–179°; $[\alpha]_D^{20}$ +100° (chloroform); M_D +430°; $\lambda_{max}^{ethanol}$ 243·5 mμ (15,900); ν_{max}^{Nujol} 3509 (OH), 1739 (acetate), 1664, 1626, 1608, 886 cm^{-1} ($\Delta^{1,4}$-diene-3-one) (Found: C, 69·52; H, 7·92. $C_{25}H_{34}O_6$ requires C, 69·74; H, 7·96%), which on treatment with potassium hydrogen carbonate was reverted to II, m.p. 194–195°; $[\alpha]_D^{20}$ +33° (chloroform); M_D +114°; $\lambda_{max}^{ethanol}$ 244·5 mμ (14,200); ν_{max}^{Nujol} 3333 (OH), 1667, 1613, 1600, 885 cm^{-1} ($\Delta^{1,4}$-diene-3-one) (Found: C, 72·53; H, 8·43. $C_{21}H_{30}O_4$ requires C, 72·80; H, 8·73%). Chromatography on Florisil of the mother liquors from the diacetate of II gave, besides an additional amount of the diacetate of II, 21-acetoxy-4-pregnene-11β,17α-diol-3,20-dione [the 21-acetate of hydrocortisone (III)], m.p. 214–216°; ν_{max}^{Nujol} 3390, 3279 (OH), 1739 (acetate), 1709 (carbonyl), 1626 cm^{-1} (Δ^4-ene-3-one) (Found: C, 67·91; H, 7·86. $C_{23}H_{32}O_6$ requires C, 68·29; H, 7·97%), which was identical in every respect with an authentic sample. The production of III by *Ps.* sp. 109 constitutes one of the rare examples of 11β-hydroxylation accomplished by micro-organisms other than fungi. The approximate ratio of the formation of II and III was 10 to 1.†

Structural assignment for II‡[3] is based upon the following facts. The colour reaction and the infra-red spectrum clearly indicated the presence of a $\Delta^{1,4}$-diene-3-one system and the absence of any isolated carbonyl group. Oxidation of II by periodic acid yielded 1,4-androstadiene-3,17-dione,[4] m.p. 137°; $[\alpha]_D^{20}$ +112° (chloroform); ν_{max}^{Nujol} 1736 (carbonyl), 1656, 1618, 1600, 890 cm^{-1} ($\Delta^{1,4}$-diene-3-one) (Found: C, 79·94; H, 8·33. $C_{19}H_{24}O_2$ requires C, 80·24; H, 8·51%), which was identical with the compound derived from 1,4-pregnadiene-17α,21-diol-3,20-dione by chromic acid oxidation. Further, the preferential reduction[5] of the 20-carbonyl group in 21-acetoxy-1,4-pregnadiene-17α-ol-3,20-dione with sodium borohydride was effected, and the product obtained after

* The numbers are of R. Takeda's collection.

† In each case a small amount of I was recovered.

‡ Sutter *et al.*[3] reported the microbiological formation of this compound, but gave only the melting points and the infra-red spectral data of the free steroid and its diacetate.

[1] R. S. Breed, E. G. D. Murray and N. R. Smith, *Bergey's Manual of Determinative Bacteriology* (7th Ed.) pp. 101, 105, 113. Williams and Wilkins Co., Baltimore (1957).

[2] R. Takeda and I. Nakanishi, *J. Fermentation Technol.* In press.

[3] D. Sutter, W. Charney, P. L. O'Neill, F. Carvajal, H. L. Herzog and E. B. Hershberg, *J. Org. Chem.* **22**, 578 (1957).

[4] H. H. Inhoffen, G. Zühlsdorff and Huang-Minlon, *Chem. Ber.* **73**, 451 (1940); H. H. Inhoffen, *Angew. Chem.* **59**, 207 (1947); J. Fried, R. W. Thomas and A. Klingsberg, *J. Amer. Chem. Soc.* **75**, 6764 (1953).

[5] J. K. Norymberski and G. F. Woods, *J. Chem. Soc.* 3426 (1955).

acetylation was found identical in all respects with the diacetate of II. The 20β-hydroxy configuration in II was assigned on the basis of the well-known mode of the sodium borohydride reduction[5,6] and of the molecular rotation data.[7]

Pseudomonas sp. 125: This organism was isolated from soil and identified as closely akin to *Pseudomonas oleovorans*.[1] Incubation of I with this organism was performed under conditions similar to those used in the case of *Ps.* sp. 109. Acetylation and subsequent chromatography over Florisil gave 21-acetoxy-1,4-pregnadiene-17α-ol-3,20-dione (the 21-acetate of IV), m.p. 215–218°; ν_{max}^{Nujol} 3333 (OH), 1739 (acetate), 1718 (carbonyl), 1658, 1613, 1600, 893 cm^{-1} ($\Delta^{1,4}$-diene-3-one) (Found: C, 71·26; H, 7·78. $C_{23}H_{30}O_5$ requires C, 71·48; H, 7·82%), and the diacetate of II, both of which were identified by rigorous comparison with respective authentic samples. The formation ratio of IV and II was roughly 2 to 1.†

Pseudomonas sp. M8: This organism was isolated from water and identified as closely akin to *Pseudomonas fluorescens*.[1] Compound I was subjected to the action of this organism under conditions similar to those used in the above cases.† Acetylation followed by chromatography on Florisil furnished 20β,21-diacetoxy-4-pregnene-17α-ol-3-one (the 20,21-diacetate of V),[8] m.p. 191–192°; $[\alpha]_D^{20}$ +133° (dioxane); M_D +575°; ν_{max}^{Nujol} 3390 (OH), 1733 (acetate), 1650, 1610 cm^{-1} (Δ^4-ene-3-one) (Found: C, 69·60; H, 8·34. $C_{25}H_{36}O_6$ requires C, 69·42; H, 8·39%). The structure of the product was confirmed by direct comparison with the compound prepared by the sodium borohydride reduction of I. Hydrolysis of the diacetate of V with potassium hydrogen carbonate afforded V, m.p. 188–189°; $[\alpha]_D^{20}$ +67° (dioxane); M_D +233°; ν_{max}^{Nujol} 3390 (OH), 1645, 1610 cm^{-1} (Δ^4-ene-3-one) (Found: C, 72·21; H, 9·18. $C_{21}H_{32}O_4$ requires C, 72·38; H, 9·26%).

Other species of *Pseudomonas* genus have also effected similar patterns of transformations. A detailed account of these findings will be published later.

Research Laboratories
Takeda Pharmaceutical Industries, Ltd.
Institute for Fermentation, Osaka

HAYAO NAWA
MASAO UCHIBAYASHI
ROKURO TAKEDA
ITARU NAKANISHI

Osaka Plant
Takeda Pharmaceutical Industries, Ltd.
Osaka
Japan

TSUNAHARU KUSAKA
JIRO TERUMICHI
MINORU UCHIDA
MICHIO KATSUMATA
KIKUKO YOSHINO
HIROSHI FUJITANI

[5] E. P. Oliveto and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 488 (1953).
[7] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1175 (1949); W. Klyne and D. H. R. Barton, *Ibid.* **71**, 1500 (1949).
[8] W. Logemann, *Naturwissenschaften* **27**, 196 (1939); C. W. Shoppee, *Helv. Chim. Acta* **23**, 925 (1940).

Papers to be published in future issues

G. BERTI: Stereochemistry of the halolactonisation reaction. The reaction of *cis*- and *trans*-stilbene-2-carboxylic acids with halogens.

A. BURAWOY, J. P. CRITCHLEY and A. R. THOMPSON: Electronic spectra of organic molecules and their interpretation—IV. Effect of terminal atoms with lone electron pairs on the K-bands of conjugated systems.

M. G. ROSSMAN and W. N. LIPSCOMB: The sesquiterpenoid iresin.

KUNIO SUKIGARA, YOSHITERU HATA, YUKIO KURITA and MASAJI KUBO: The dipole moments and the structures of chloro- and bromo-crotonolactones.

C. ENZELL and H. ERDTMAN: The chemistry of the natural order cupressales—XXI: Cuparene and cuparenic acid, two sesquiterpenic compounds with a new carbon skeleton.

J. S. BRIMACOMBE, A. B. FOSTER, M. STACEY and D. H. WHIFFEN: Aspects of stereochemistry—I: Properties of reactions of some diols.

T. R. GOVINDACHARI, M. V. LAKSHIMIKANTHAM, K. NAGARAJAN and R. B. PAI: Chemical examination of Tylophora asthmatica—II.

V. K. AHLUWALIA, A. C. MEHTA and T. R. SESHADRI: Constitution of dalbergin—IV: A novel transformation of O-methyldalbergin.

R. ANEJA, S. K. MUKERJEE and T. R. SESHADRI: A study of the origin and modification of the C_6 unit in plant products—new synthesis of angeliciu and psoralen.

V. HEROUT and V. SÝKORA: The chemistry of cadinenes and cadinols.

E. BERNATEK: Ozonolysis of the naphthaquinones—I: Onzonolysis of 1 : 4-naphthaquinone in chloroform.

R. P. EVSTIGNEEVA and N. A. PREOBRAZHENSKY: Synthesis of ipecacuanha alkaloids.

B. FRYDMAN, R. BENDISCH and V. DEULOFEU: A synthesis of laudamine and (±) pseudocodamine resolution in the optical isomers.

J. N. T. GILBERT and D. W. MATHIESON: Cucurbitacin E. Some preliminary observations.

P. N. RAO and K. RAMAN: A stereospecific synthesis of (±) ferruginol.

J. F. FORD, R. C. PITKETHLY and V. O. YOUNG: Stereochemistry of the co-oxidation products of indene and thiophenol.

L. VELLUZ, B. GOFFINET et G. AMIARD: Sur le comportement photochimique des 19-nor $\Delta^{5,7}$-steroides.

CARL DJERASSI, O. HALPERN, D. I. WILKINSON and E. J. EISENBRAUN: Macrolide antibiotics—VIII: The absolute configuration of certain centers in neomethycin, erythromycin and related antibiotics.

E. C. KOOYMAN and G. C. VEGTER: Bicyclanes—I. The halogenation of 2:2:1-bi*cyclo*heptane (norbornane).

SHIGEHIKO SUGASAWA and RYUJI TACHIKAWA: Extension of Bischler–Napieralski reaction—I. Synthesis of *iso*quinoline derivatives. A synthesis of *rac*.-amorphine dimethylether.

F. LAMB and H. SUSCHITZKY: Studies in the xanthone series—III: Preparation and reactions of 1-acetyl-2-hydroxyxanthone.

A. QUILICO, F. PIOZZI, M. PAVAN and E. MANTICA: The structure of pereplanetin.

F. SONDHEIMER and Y. KLIBANSKY: Synthesis of 3β-hydroxy analogues of steroidal hormones, a biologically active class of compounds.

P. MIROSEVIC-SORGO and B. C. SAUNDERS: Toxic fluorine compounds containing the C–F link—X. Rupture of the C–F link by alkali and other reagents.

R. B. WOODWARD and T. J. KATZ: The mechanism of the Diels–Adler reaction.

K. BALENOVIĆ and N. BREGANT: Absolute configuration of α-methyl-β-alanine.

SHIGEHIKO SUGASAWA and S. USHIODA: Extension of the Bischler–Napieralski reaction—II. Synthesis of pyrroline derivatives.

J. W. CORNFORTH, R. H. CORNFORTH, Z. PELTER, M. G. HORNING and G. POPJÀK: Studies on biosynthesis of cholesterol—7. Rearrangement of methyl groups during enzymic cyclisation of squalene.

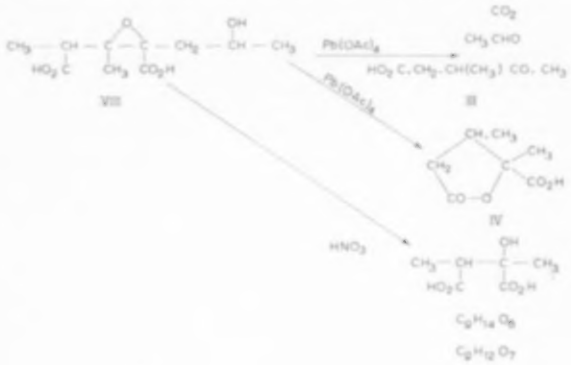
A. BURAWOY and J. P. CRITCHLEY: Electronic spectra of organic molecules and their interpretation—V. Effect of terminal groups containing multiple bonds on the K-bands of conjugated systems.

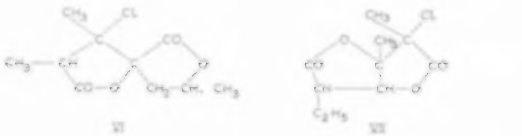
E. M. KOSOWER and D. C. REMY: The effect of a positive charge on a $\pi \leftarrow \pi^*$-transition.

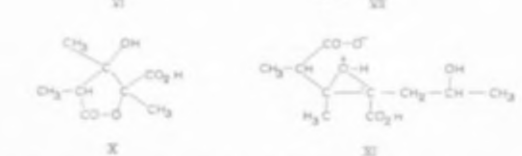
ERRATA

1. R. B. Bradbury, *Tetrahedron* **2**, 363–365 (1958).

Formulae (III) to (XI) were omitted from this article. They are published below.







2. G. Wittig und U. Schöllkopf, *Tetrahedron* **3**, 91–93 (1958).
Since publication, the formula on p. 91 has been altered to
$[C_6H_5.CH_2—Br—C_6H_5]^-Li^+$.

3. Pierre Crabbé, Guy Ourisson et Takeyoshi Takahashi, *Tetrahedron* **3**, 279–302, 303–309 (1958).

p. 284: la légende du Tableau 4 devrait être placée sous ce Tableau, au bas de la page.

p. 285: la légende du Tableau 5 devrait être placée sous ce Tableau, p. 286, à la place des schémas VII et E, qui devraient être intercalés dans le dernier paragraphe de la p. 285.

p. 287: les schémas conformationnels sont respectivement (F) (à gauche) et (G) (à droite).

p. 291: le schéma structural est (J), et devrait être inséré 12 lignes à partir du bas de la page.

p. 303: les trois schémas structuraux devraient être insérés dans les cases de la colonne de gauche du Tableau 1, p. 304; les lettres A, B, C sont à supprimer.

Tetrahedron, 1958, Vol. 4, pp. 205–212. Pergamon Press Ltd., London

EXTENSION OF BISCHLER–NAPIERALSKI REACTION—I

SYNTHESIS OF *ISO*QUINOLINE DERIVATIVES: A SYNTHESIS OF *RAC.*-APOMORPHINE DIMETHYL ETHER

SHIGEHIKO SUGASAWA and RYUJI TACHIKAWA
Pharmaceutical Institute, University of Tokyo, Tokyo, Japan

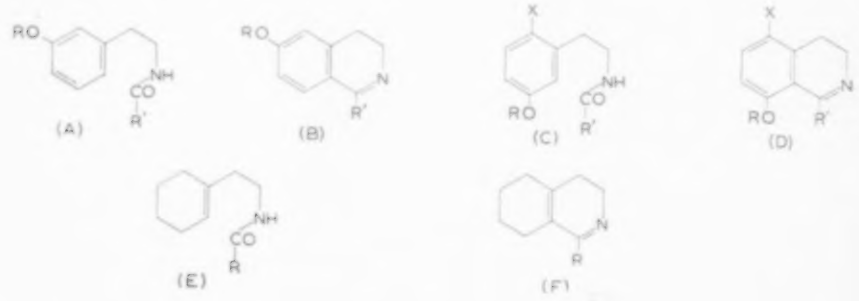
(*Received* 28 *March* 1958)

Abstract—The scope of Bischler-Napieralski reaction has now been extended to include acyl *cyclo*hexa-1:4-dienylethylamide types, which cyclise smoothly to yield various *iso*quinolines after dehydrogenation. 1-(2-Nitro-3:4-dimethoxybenzyl)-3:4-dihydro*iso*quinoline, hitherto difficultly accessible, could be prepared and converted to *rac.*-apomorphine dimethyl ether.

THE Bischler–Napieralksi reaction[1] in modified forms has been extensively used for the cyclisation of 3-alkoxyphenethylamides (A) to furnish 6-alkoxy*iso*quinolines (B). When the *para*position to the alkoxy group in (A) is occupied, as in (C), the cyclisation occurs at the *ortho*position to form 8-alkoxy*iso*quinoline derivatives (D).[2]

The cyclisation of simple phenethylamides having no activating group takes place with difficulty to give poor yields of the products. Thus the synthesis of apomorphine dimethyl ether has been the subject of long dispute by various workers, to which the recent communication by Hey and Palluel,[3] which appeared during our present work, seems to have offered a solution.

In their paper published in 1950, Schnider and Hellerbach[4] reported an improved synthesis of 1-substituted 3:4:5:6:7:8-hexahydro*iso*quinoline derivatives (F), useful intermediates for the preparation of morphinans from acyl *cyclo*hexen-1-ylethylamides (E) by treating with phosphoryl chloride in boiling benzene.



This would seem to suggest that the Bischler–Napieralski reaction takes place toward a carbon-to-carbon double bond, provided the double bond is suitably located with regard to the acyl amido-group. This was verified by synthesising 1-methyl- and

[1] W. M. Whaley and T. R. Govindachari, *Organic Reactions* (Ed.-in-Chief Roger Adams) Vol. VI, p. 74. Wiley, New York (1951).
[2] S. Sugasawa and H. Shigehara, *Ber. Dtsch. Chem. Ges.* **74**, 459 (1941).
[3] D. H. Hey and A. L. Palluel, *Proc. Chem. Soc.* 7 (1957).
[4] O. Schnider and J. Hellerbach, *Helv. Chim. Acta* **33**, 1437 (1950).

1-benzyl-*iso*quinolines (Va) and (Vb) from aceto- and phenylaceto-*cyclo*hexa-1:4-dienlyethylamides (IIa) and (IIb) by refluxing with phosphoryl chloride in benzene solution followed by dehydrogenation.

Thus phenethylamine was reduced according to Birch as modified by Wilds and Nelson[5] to furnish *β-cyclo*hexa-1:4-dienylethylamine (I), which was then acylated to the corresponding amides (IIa) and (IIb). The absence of aromatic contamination in both (I) and (II) was confirmed by their ultra-violet spectra (Fig. 1). When (IIa) was

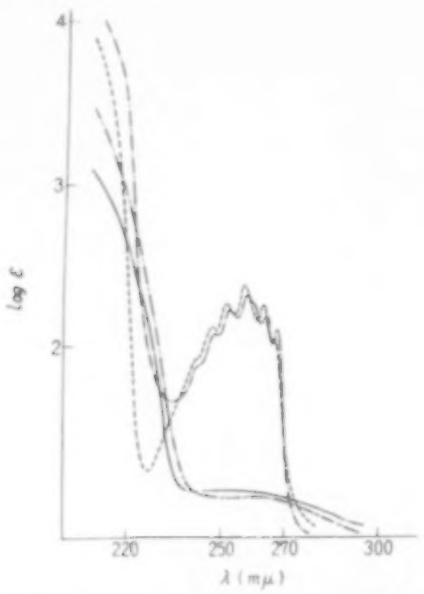


FIG. 1. Ultra-violet spectra of amines and their acetyl derivatives.
- - - - - - - - - -Phenethylamine
———————— Amine (I)
—·—·—·— Acetophenethylamide
··—··—·· Amide (IIa).

refluxed with phosphoryl chloride in benzene, cyclisation proceeded smoothly to yield a viscous syrup b.p. 95–96°/4·5 mm, but the product was not the expected (IIIa). The picrate melted over a range 178–187°, which was raised to 190–191° and this was not depressed when admixed with the picrate of 1-methyl-3:4-dihydro*iso*quinoline (IVa) m.p. 191–193°, prepared by cyclising acetophenethylamide. The methiodide of the above-mentioned syrup separated first as a glass, which crystallised and melted at 193–195°. (IVa) gave at once a crystalline methiodide, which melted at 193–195° alone or admixed with the above sample.

These facts would seem to show that the cyclised product, b.p. 95–96°/4·5 mm, is impure 1-methyl-3:4-dihydro*iso*quinoline (IVa), rather than the crude 1-methyl-3:4:5:8-tetrahydro*iso*quinoline (IIIa),* which probably owed its formation to the latter through disproportionation during the cyclisation reaction or air-oxidation during working-up.

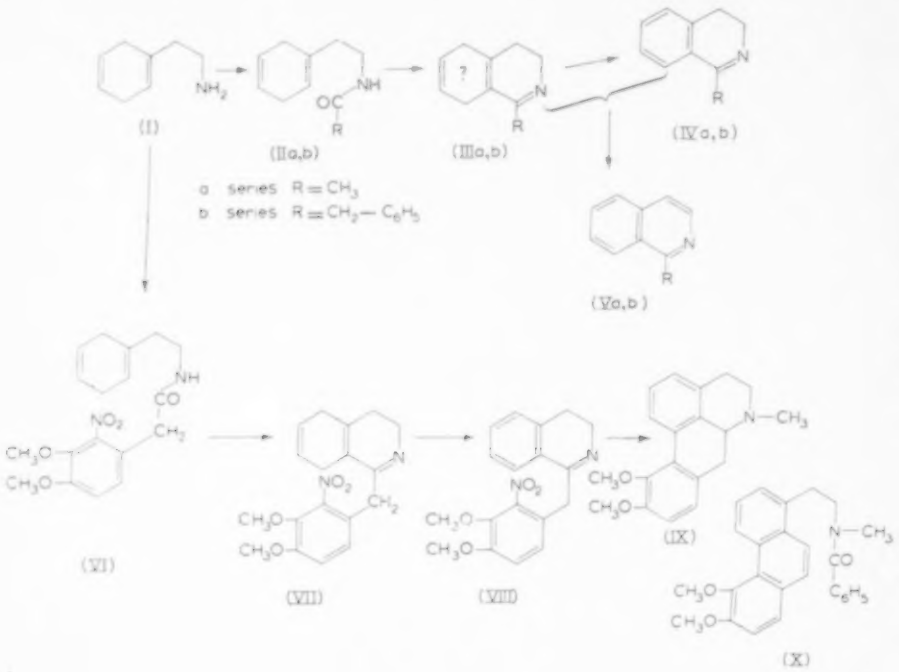
* Fig. 2 shows the ultra-violet absorption curves of the pure (IVa) and the oil of b.p. 95–96°/4·5 mm. The somewhat lower intensity at λ_{max} 248 mμ of the latter compound is probably due to the presence of non-aromatic contamination.

[5] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5630 (1953).

The oil, b.p. 95–96°/4·5 mm, was treated with palladium–carbon in boiling *p*-cymene, when 1-methyl*iso*quinoline (Va) was obtained, which was identified by comparison with an authentic specimen.

1-Benzyl*iso*quinoline (Vb) was also prepared from phenylaceto*cyclo*hexa-1:4-dienylethylamide (IIb).

This method was now successfully extended to synthesise *rac.*-apomorphine dimethyl ether (IX).



The amine (I) was acylated with the chloride of 2-nitro-3:4-dimethoxyphenylacetic acid, prepared according to Pschorr and Sumuleanu[6] and Kay and Pictet[7] to give a crystalline amide (VI), m.p. 90–91·5°. The cyclisation of the latter was effected with phosphoryl chloride in boiling benzene to give an uncharacterised intermediate (VII) in about 70 per cent yield. The dehydrogenation of this compound to 1-(2-nitro-3:4-dimethoxybenzyl)-3:4-dihydro*iso*quinoline (VIII) was achieved by boiling with palladium–carbon in xylene, which melted at 127–128° alone or admixed with an authentic specimen of (VIII).† The conversion of (VIII) to *rac.*-apomorphine dimethyl ether (IX) gave a faint-yellow viscous syrup, b.p. 186–190°/0·01 mm (cf. Figs. 3 and 4). For further characterisation this was benzoylated according to Späth and Hromatoka,[8]

† Prepared according to Späth in small yield by cyclising 2-nitro-3:4-dimethoxyphenylacetophenethylamide with phosphorous pentoxide in boiling xylene. A large quantity of the neutral product of m.p. 124–125° (cf. Hey and Palluel[9]) was recovered.

[6] R. Pschorr and C. Sumuleanu, *Ber. Dtsch. Chem. Ges.* **32,** 3405 (1899).
[7] F. W. Kay and A. Pictet, *J. Chem. Soc.* **103,** 947 (1913).
[8] E. Späth and O. Hromatoka, *Ber. Dtsch. Chem. Ges.* **62,** 326 (1929).

when 5:6-dimethoxy-1-(benzamethylamidoethyl)phenathrene (X), m.p. 163–164·5°, was obtained.

On the other hand *l*-apomorphine was methylated with diazomethane as usual and the resulting dimethyl ether was benzoylated as above to yield (X), which was proved to be identical with the above obtained product.

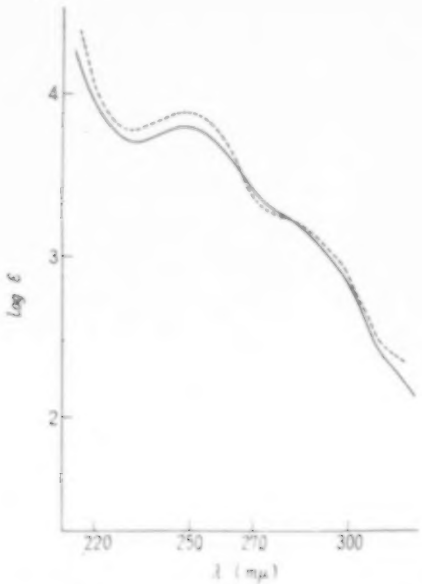


FIG. 2. Ultra-violet spectra of pure (IVa) and the oil of b.p. 95–96°/4·5 mm.
- - - - - - - - - Pure (IVa)
———— Oil of b.p. 95–96°/4·5 mm.

The work will be extended to include other $\gamma\delta$-unsaturated acyl amides for preparing various nitrogen heterocyclic compounds.

EXPERIMENTAL

*β-cyclo**Hexa*-1:4-*dienylethylamine* (I). Liquid ammonia (150 ml) was added to phenethylamine (12 g) in absolute ethanol (45·6 g), cooled in a solid carbon dioxide–ethanol bath. Metallic lithium (7 g) was now added to this mixture in small portions with stirring. The added metal was rapidly consumed and the mixture developed a blue colour after 30 min. The addition of lithium was now regulated to maintain the blue colour. After all the metal had been added (2 hr) the stirring was continued for 30–40 min until decolorisation occurred. Ammonia was now evaporated and the residue was treated with cold water (300 ml) with cooling, and an oily layer separated, which was taken up in ether and dried, and the solvent was evaporated in an atmosphere of nitrogen. The product was obtained as a colourless oil, b.p. 61–62°/4·5 mm, and is a strong base absorbing carbon dioxide to form a salt. The yield of distilled product was 10·8 g (88·5 per cent).

Aceto-(β-cyclohexa-1:4-*dienyl)ethylamide* (IIa). The base (I) (3·5 g) in benzene (30 ml) was acylated with acetyl chloride (2·4 g) in sodium hydroxide solution. The

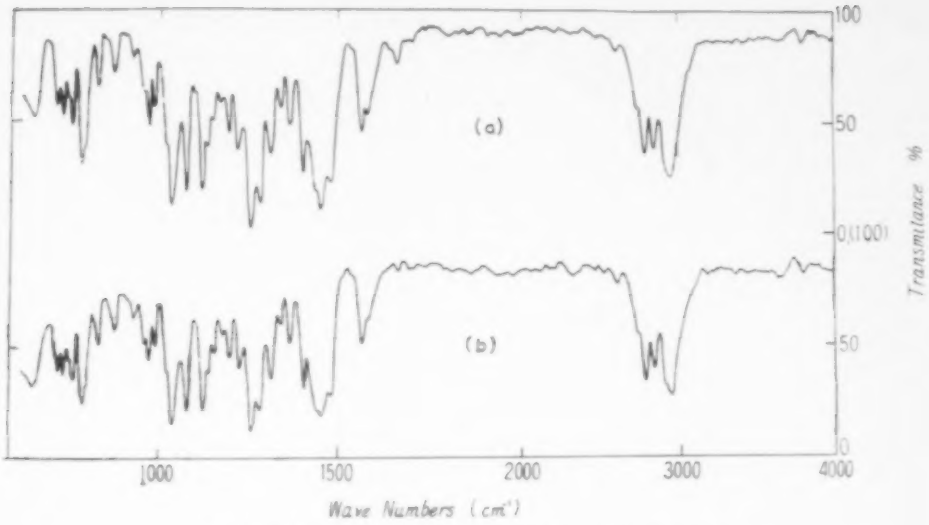


FIG. 3. Infra-red spectra of *rac.*-apomorphine dimethyl ether (a) and L-apomorphine dimethyl ether (b).

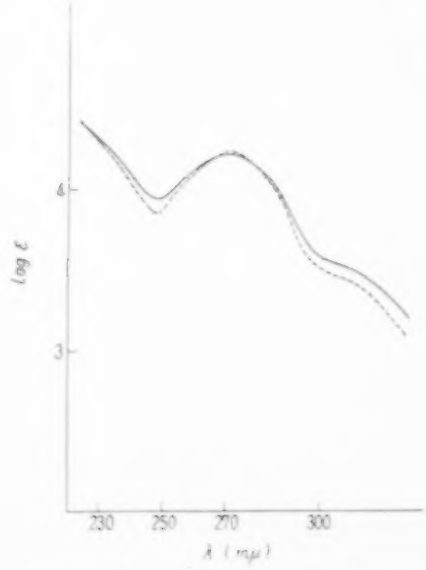


FIG. 4. Ultra-violet spectra of *rac.*- and L-apomorphine dimethyl ether.
——— *rac.*-compound
- - - - - - - L-compound.

crude amide (4·7 g, 94·8 per cent) was obtained as a glass, which solidified on standing, and, when purified from *n*-hexane, formed colourless needles, m.p. 46·5–47·5° (Found: C, 72·6; H, 8·9; N, 8·5. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1; N, 8·5 per cent).

Cyclisation of (IIa). The amide (2 g) in pure benzene (20 ml) was mixed with freshly purified phosphoryl chloride (3 ml) and refluxed on a steam-bath. A copious evolution of hydrogen chloride was observed, which ceased after 30 min. On cooling sufficient light petroleum was added to cause a reddish brown layer to separate, and the supernatant layer was discarded. The residue was dissolved in dilute hydrochloric acid and the solution shaken once with benzene to remove non-basic contaminants. The acid layer was now treated with sodium carbonate solution, and the oily layer which separated was collected in benzene, washed and dried, and the solvent was removed by distillation in an atmosphere of nitrogen. The residue distilled at 95–96° under 4·5 mm, as a clear colourless oil, which gradually became brown on exposure to air. The yield of the distilled product was 1·51 g (85·7 per cent). The picrate separated as yellow crystals, m.p. 178–187°, which was raised to 190–191° on being purified by repeated crystallisation from acetone, when yellow prisms were obtained. The m.p. of the prisms was not depressed on admixture with an authentic picrate of 1-methyl-3:4- dihydro*iso*quinoline (IVa).

1-*Methyliso*quinoline (Va). The foregoing cyclised product (0·2 g) in *p*-cymene (5 ml) was refluxed with 30% Pd–C (0·1 g) in an oil-bath for 2 hr. On cooling, the catalyst was filtered off and the filtrate was repeatedly extracted with dilute hydrochloric acid. The combined acid extracts were then made alkaline with sodium hydroxide solution and the base was collected in benzene, washed and dried, and the solvent was evaporated to leave a faint-yellow oily base, which amounted to 0·17 g, or 86·3 per cent. This was characterised as the picrate, which formed yellow needles, m.p. 210–212°, from acetone and was identified with an authentic picrate of 1-methyl*iso*quinoline.

The hydrochloride was also prepared, which crystallised in colourless needles, m.p. 185–187°, from acetone–ethanol and was proved to be identical with 1-methyl-*iso*quinoline hydrochloride.

*Phenylaceto-β-*cyclo*hexa*-1:4-*dienyl*)*ethylamide* (IIb). This was prepared as (IIa). The crude product was obtained as a white solid (95·2 per cent), and when purified from benzene–light petroleum formed colourless plates, m.p. 94–95° (Found C: 79·2; H, 7·7; N, 6·0. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9; N, 5·8 per cent). The cyclisation of this amide and working-up of the product were carried out as described above, to give a brown oil, which distilled at 145–148°/0·1 mm; the yield was 79 per cent. The picrate separated as a yellow solid, m.p. 164–168°, which was raised to 173–175° on purification from acetone, when yellow plates were obtained, and the m.p. was not depressed on admixture with the picrate of 1-benzyl-3:4-dihydro*iso*-quinoline.

1-*Benzyliso*quinoline (Vb). The foregoing base, b.p. 145–148°/0·1 mm, (0·3 g) in *p*-cymene (10 ml) was refluxed with 30 per cent Pd–C (0·1 g) in an atmosphere of nitrogen for 2 hr and then worked up as described above. The crude product was obtained as a brown syrup (0·21 g, 70·6 per cent), which distilled at 164–166°/0·1 mm to give a faint yellow viscous oil, which solidified on being agitated and was purified from *n*-hexane, to give colourless prisms, m.p. 51–52°, which were identified by direct comparison with 1-benzyl*iso*quinoline.

The picrate formed yellow prisms, m.p. 181–183°, from ethanol and the hydrochloride separated in colourless needles, m.p. 170–172°, from acetone–ethanol. The two compounds were also identified with the corresponding authentic specimens from 1-benzyl*iso*quinoline.

2-*Nitro*-3:4-*dimethoxyphenylaceto*-(*β*-cyclo*hexa*-1:4-*dienyl*)*ethylamide* (VI). The base (I) (1·3 g) in pure benzene (30 ml), mixed with 5 per cent sodium hydrogen carbonate solution (50 ml), was acylated with 2-nitro-3:4-dimethoxyphenylacetyl chloride* (2·6 g) dissolved in 30 ml of pure benzene with stirring and cooling at 5°. After stirring for an additional 2 hr, the supernatant benzene layer was washed successively with dilute hydrochloric acid, sodium hydrogen carbonate solution and water and then dried, and the solvent was removed *in vacuo*. The residual viscous brown syrup was dissolved in a small amount of benzene and filtered through a short alumina column. A faint yellow glass thus obtained amounted to 3·4 g (92·9 per cent), which solidified. When purified from benzene–light petroleum, colourless needles were obtained, m.p. 90–91·5° (Found: C, 62·2; H, 6·3; N, 7·9. $C_{18}H_{22}O_5N_2$ requires C, 62·4; H, 6·4; N, 8·1 per cent).

Cyclisation of the amide (VI). A mixture of the foregoing amide (2 g), absolute benzene (50 ml) and phosphoryl chloride (2 ml) was refluxed on a steam-bath. A copious evolution of hydrogen chloride occurred and ceased after about 30 min, to give a dark-brown solution. Benzene and excess of phosphoryl chloride were removed in a hydrogen atmosphere under reduced pressure, and the resulting dark-coloured residue was dissolved in 10 per cent hydrochloric acid, leaving some undissolved material, which was removed by shaking with benzene. The clear acid solution was treated with decolorising charcoal and then basified with sodium carbonate solution, and the free base that separated was dissolved in benzene, washed and dried, and the solvent was removed in an atmosphere of hydrogen under reduced pressure. A brown syrup thus obtained weighed 1·45 g (76·5 per cent), which was again dissolved in benzene and filtered through an alumina column. The product was now obtained as a solid and was purified from light petroleum to give yellow prisms 1·27 g, or 66·9 per cent, m.p. 112–113°. Though the m.p. of this compound was sharp, it did not give satisfactory analyses for (VIII) (Found: C, 65·5; 65·5; H, 5·2; 5·1; N, 8·5. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1; N, 8·5 per cent).

1-(2-*Nitro*-3:4-*dimethoxybenzyl*)-3:4-*dihydroisoquinoline* (VIII). For the partial dehydrogenation of (VII) the following procedure was found to be satisfactory. The base (1·2 g), m.p. 112–113°, in xylene (30 ml) was refluxed with 30 per cent Pd–C (0·2 g) in an atmosphere of nitrogen for 3 hr. On cooling, the filtrate from the catalyst was evaporated *in vacuo* to leave a yellow viscous syrup, which was again dissolved in pure benzene and purified through an alumina column. From the filtrate a yellow solid was recovered (1·05 g, 88 per cent), which separated from acetone in pale-yellow prisms, m.p. 127–128° (Found: C, 66·5; H, 5·3; N, 8·3. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5; N, 8·6 per cent). The methiodide was obtained as yellow needles from methanol, m.p. 201–203° (dec.).

rac.-*Apomorphine dimethyl ether* (IX). This was prepared by the usual method and was obtained as a very viscous pale-yellow syrup, b.p. 186–190°/0·01. The yield of

* 2-Nitro-3:4-dimethoxybenzyl alcohol, the intermediate for this chloride, was prepared from the corresponding aldehyde by the crossed Cannizarro method.

the distilled product was 49·6 per cent based on 1-(2-nitro-3:4-dimethoxybenzyl)-2-methyl-1:2:3:4-tetrahydro*iso*quinoline.

5:6-*Dimethoxy*-1-(*benzamethylamidoethyl*)*phenanthrene* (X). *rac.*-Apomorphine dimethyl ether was boiled with benzoyl chloride for 1 hr according to the method of Späth. The benzoyl derivative (X) formed pale-yellow minute needles from *n*-hexane. The m.p. 164–165° was not depressed on admixture with an authentic specimen of the same m.p. prepared from L-apomorphine dimethyl ether (Found: C, 77·9; H, 6·4; N, 3·8. $C_{26}H_{25}O_3N$ requires C, 78·2; H, 6·3; N, 3·5 per cent).

Tetrahedron, 1958, Vol. 4, pp. 213–222. Pergamon Press Ltd., London

OZONOLYSIS OF NAPHTHOQUINONES—I

OZONOLYSIS OF 1:4-NAPHTHOQUINONE IN CHLOROFORM

ERLING BERNATEK
Universitetets Kjemiske Institutt Blindern-Oslo, Norway

(*Received* 3 *April* 1958)

Abstract—During ozonisation of 1:4-naphthoquinone in chloroform at −5 to −8° about 70 per cent undergoes anomalous ozonolysis forming phenylglyoxal-*o*-carboxylic acid and probably carbon monoxide. The remaining 30 per cent forms a normal ozonide which rearranges to a mixed anhydride of formic acid and phenylglyoxal-*o*-carboxylic acid. Sodium iodide reduction of the normal ozonide produces *o*-phenylenediglycolaldehyde. An intramolecular benzoin condensation of this substance is discussed.

NAPHTHOQUINONES (especially the 1:4- or α-isomers) occur widely in nature and can be isolated from varied and unexpected sources. The yellow pigment lawson, (2-hydroxy-1:4-naphthoquinone) can be extracted from the leaves of *Lawsonia inermis*; phthiocol (2-hydroxy-3-methyl-1:4-naphthoquinone) has been isolated from *Mycobacterium tuberculosis*; echinochrome A (3-ethyl-2:5:6:7:8-pentahydroxy-1:4-naphthoquinone) occurs as a pigment in the eggs of *Arbacia punctulata* and other sea-urchins. Among other notable naturally occurring 1:4-naphthoquinones are vitamins K_1 and K_2.

Several naphthoquinones isolated are complex, and the elucidation of their structures present difficulties. In the determination of molecular constitution, ozonolysis occupies a prominent place, but only a few instances occur in the literature where naphthoquinones have been ozonised. Majima and Kuroda[1] ozonised shikonin (a dark red pigment from the roots of *Lithospermum erythrorhizon*) 2-(1-hydroxy-4-methyl-3-pentenyl)-5:8-dihydroxy-1:4-naphthoquinone(I), as well as its triacetyl

I

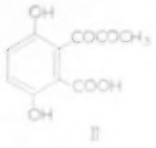
derivative. A pigment from the roots of *Alkanna tinctoria*, alkannin was ozonised by Dieterle, Salomon and Nosseck[2] who only identified oxalic acid. Later alkannin and its triacetyl derivative were ozonised by Brockmann[3] and its methyl ether by Raudnitz and Stein.[4] Brockmann also showed that alkannin and shikonin were optical isomers, alkannin being laevorotatory and shikonin dextrorotatory. In connection with the work on alkannin Raudnitz and Behrens[5] ozonised naphthazarin and two of its homologues.

Majima and Kuroda ozonised shikonin in a mixture of chloroform and water and isolated in this case only decomposition products of the side chain namely, acetone

[1] R. Majima and C. Kuroda, *Acta Phytochim., Tokyo* **1**, 43 (1922).
[2] H. Dieterle, A. Salomon and E. Nosseck, *Ber. Dtsch. Chem. Ges.* **64**, 2086 (1931).
[3] H. Brockmann, *Liebigs Ann.* **521**, 1 (1936).
[4] H. Raudnitz and W. Stein, *Ber. Dtsch. Chem. Ges.* **68**, 1479 (1935).
[5] H. Raudnitz and F. Behrens, *Ber. Dtsch. Chem. Ges* **68**, 1484 (1935).

peroxide and, on further oxidation with potassium permanganate, succinic acid. Triacetyl shikonin was ozonised in dry chloroform followed by hydrolysis of the ozonide with hot water. Again acetone peroxide was isolated and in addition 3:6-dihydroxyphthalic acid, which is of interest because it results from the cleavage of the double bond in the quinone ring. The degradation has, however, gone rather far as only two of the four extrabenzenoid carbon atoms of the ring are left.

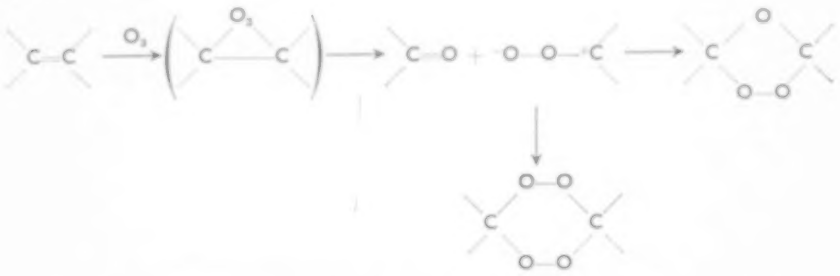
Of immediate interest is the work done by Raudnitz and Behrens on ozonisation of naphthazarin, methylnaphthazarin (2-methyl-5:8-dihydroxy-1:4-naphthoquinone) and a dimethylnaphthazarin with methyl groups in 2-position and 6- or 7-position. Naphthazarin yielded 3:6-dihydroxyphthalic acid where we again may observe a rather drastic degradation of the quinone ring. Methyl naphthazarin gave a substance which on the basis of its composition $C_{10}H_8O_6$ was assigned the structure(II) methyl



II

(3:6-dihydroxy-2-carboxy) glyoxal. Dimethylnaphthazarin gave a homologue of (II) with methyl in position 4 or 5. In none of the above-mentioned ozonolyses was the reaction between the quinone and ozone or reactions of the ozonide studied.

In the Criegee mechanism for ozonide formation,[6,7] the initial (but unspecified) adduct of ozone to the double bond breaks down to a carbonyl compound and a zwitterion. These two fragments will in some cases recombine to form a true ozonide, but in other cases the zwitterion may dimerise (or polymerise) leaving the carbonyl fragment as such:



Other authors have discussed whether the addition of ozone to a double bond follows the rule of Markownikoff.[8,9] 1:4-Additions of ozone to such conjugated systems as furans and pyrroles have been investigated,[10] and attempts have been made to elucidate the mechanism of the initial attack of ozone on unsaturated systems and the nature of the primary addition compound.[11,12,13]

[6] R. Criegee, *Fortschr. Chem. Forsch.* **1**, 528 (1949/1950)
[7] R. Criegee, A. Kerckow and H. Zinke, *Ber. Dtsch. Chem. Ges.* **88**, 1878. (1955).
[8] P. S. Bailey, *Ber. Dtsch. Chem. Ges.* **88**, 795 (1955).
[9] J. Meinwald, *Ber. Dtsch. Chem. Ges.* **88**, 1889 (1955).
[10] P. S. Bailey and H. D. Colomb, *J. Amer. Chem. Soc.* **79**, 4238 (1957).
[11] P. S. Bailey and S. S. Bath, *J. Amer. Chem. Soc.* **79**, 3120 (1957).
[12] P. S. Bailey and J. B. Ashton, *J. Org. Chem.* **22**, 98 (1957).
[13] P. S. Bailey, *Chem. & Ind.* 1148 (1957).

Ozone is classified as a "double bond reagent", by Badger,[14] and the mode of attack has been discussed by Brown[15] who assumes a one-stage process where ozone reacts with the bond of the lowest bond localisation energy. Wibaut and collaborators[16] have brought forth seemingly contrasting evidence for the electrophilicity of ozone. This would then imply a two-stage process with an initial attack on the carbon atom with the lowest atom localisation energy. These conflicting views seem now to have been reconciled by Bailey.[13]

In naphthoquinone(III) the reactivity towards ozone is dependent upon the localisation energy of the 2:3-double bond.

III IV V

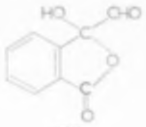
Assuming a complete localisation of the π-electrons in the idealised transition state IV and following the simple treatment of Kooyman and Ketelaar[17] an estimate could be obtained by subtracting the resonance energy of the "residual" molecule (here represented by phthalaldehyde V) from that of the "original" molecule(III). Unfortunately, the necessary thermochemical data are not available in the literature. The small resonance energy in *p*-benzoquinone is about 4 kcal/mole,[18] therefore the carbon–carbon double bonds in this molecule must be almost completely localised. Similarly, in the quinoid double bond of (III) a rather low localisation energy may be expected. This is in accordance with a qualitative observation made during ozonisation experiments with naphthoquinone. When ozone reacts with naphthoquinone in chloroform at -5 to $-8°$ a little ozone escapes indicating a slow reaction. This is not the case when ozonising a purely olefinic substance, but on the other hand, the volume of escaping ozone is not as large as when a purely aromatic substance is ozonised.

The ozonide of naphthoquinone does not separate during the reaction, but a viscous syrup is obtained after addition of petrol ether and this substance decomposes rapidly with the evolution of gas and acrid fumes in which carbon monoxide can be detected. The syrupy substance burns violently and liberates iodine from sodium iodide in glacial acetic acid, but due to its instability no attempt was made to determine the content of active oxygen. When kept under the solvent at about $+4°$ for some days it crystallises and carbon monoxide can be detected above the liquid. The crystalline substance does not contain active oxygen and is a monobasic acid, $C_9H_6O_4$. It reduces Tollens reagent but not Fehlings solution and gives a sparingly soluble derivative with *o*-phenylenediamine hydrochloride. This derivative, white needles, is a monobasic acid

[14] G. M. Badger, *Quart. Rev. Chem. Soc.* **5**, 155 (1951).
[15] R. D. Brown, *Quart. Rev. Chem. Soc.* **6**, 63 (1952).
[16] P. W. Haayman and J. P. Wibaut, *Rec. Trav. Chim.* **60**, 842 (1941); J. P. Wibaut and E. C. Kooyman, *Ibid.* **65**, 141 (1946); J. P. Wibaut and J. Van Dijk, *Ibid.* **65**, 413 (1946); J. Van Dijk, *Ibid.* **67**, 945 (1948); J. P. Wibaut, F. L. J. Sixma, L. W. F. Kampschmidt and H. Boer, *Ibid.* **69**, 1355 (1950); H. Boer, F. L. J. Sixma and J. P. Wibaut, *Ibid.* **70**, 509 (1951); F. L. J. Sixma, H. Boer and J. P. Wibaut, *Ibid.* **70**, 1005 (1951); J. P. Wibaut and F. L. J. Sixma, *Ibid.* **71**, 761 (1952); F. L. J. Sixma, *Ibid.* **71**, 1124 (1952); L. W. F. Kampschmidt and J. P. Wibaut, *Ibid.* **73**, 431 (1954); J. P. Wibaut and H. Boer, *Ibid.* **74**, 241 (1955).
[17] E. C. Kooyman and J. A. A. Ketelaar, *Rec. Trav. Chim.* **65**, 859 (1946).
[18] G. W. Wheland, *Resonance in Organic Chemistry* p. 99. New York (1955).

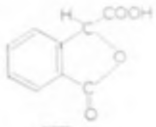
$C_{15}H_{10}O_2N_2$ related to quinoxaline. By cautious oxidation with nitric acid, $C_9H_6O_4$ was converted to phthalonic acid. This evidence strongly suggests that $C_9H_6O_4$ is phenylglyoxal-*o*-carboxylic acid (VI), or by analogy with phthalaldehydic acid and its

VI



VII

derivatives[19] may have a phthalide structure (VII). It is acidic and reacts with an ethereal solution of diazomethane with evolution of nitrogen. The infra-red spectrum of $C_9H_6O_4$ shows two bands at 1700 and 1722 cm^{-1} due to the aldehydic and ketonic carbonyl groups. A strong carboxyl frequency (deformation frequency) occurs at 1270 cm^{-1}. For comparison the spectra of phthalide carboxylic acid and phthalide were recorded and showed strong lactone bands at 1765 and 1740 cm^{-1} respectively. In this region the substance only shows a not very prominent shoulder. It may therefore be concluded that the acid $C_9H_6O_4$ occurs as (VI) but is perhaps in equilibrium with small amounts of (VII). This seems to be borne out by observations made during sublimation *in vacuo* at 130-140° (bath temperature). A gas is evolved and a white, macrocrystalline, substance sublimes, which was shown to be a mixture of phthalide

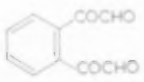


VIII

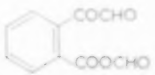
and phthalide carboxylic acid (VIII). The latter may result from thermal rearrangement of (VII), and phthalide by decarboxylation of (VIII). The equilibrium between (VI) and (VII) must therefore be displaced towards (VII) at higher temperatures. The presence of (VI) and formic acid after ozonolysis of naphthoquinone was confirmed (see experimental section). An attempt to prepare (VI) by oxidation of acetophenone *o*-carboxylic acid with selenium dioxide was unsuccessful (compare Sato and Ohta[20]), the product of the oxidation was phthalide carboxylic acid.

Assuming the structure (IX) for the ozonide of naphthoquinone hydrolysis would give *o*-phenylenediglyoxal (X) and hydrogen peroxide, but (X) has not been isolated and traces only of hydrogen peroxide were detected during the treatment of the ozonide with water.

IX



X



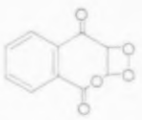
XI

Ozonides can, like other peroxidic compounds, undergo rearrangements where one of the "peroxidic" oxygen atoms is interposed between two carbon atoms. In this

[19] D. D. Wheeler, D. C. Young and D. S. Erley, *J. Org. Chem.* **22**, 547 (1957).
[20] T. Sato and M. Ohta, *Bull. Chem. Soc. Japan* **28**, 480 (1955).

case such a rearrangement would lead to the structure(XI) which is a mixed anhydride of phenylglyoxal-*o*-carboxylic and formic acids. Treatment with water would give both acids while the substance itself under anhydrous conditions probably decomposes with evolution of carbon monoxide and formation of phenylglyoxal-*o*-carboxylic acid. Such decompositions of mixed anhydrides of formic acid with formation of carbon monoxide are well known. From the experimental data it may be assumed that (IX) is formed which rearranges into the mixed anhydride (XI) followed by decomposition to phenylglyoxal-*o*-carboxylic acid (VI) and carbon monoxide. When the ozonisation is complete, some of the ozonide has rearranged and decomposed. Addition of water will hydrolyse the anhydride thus accounting for formic acid. If the ozonisation mixture is left the remaining ozonide rearranges and evolves further amounts of carbon monoxide. After 5 hr when the mixture contained no more active oxygen, 6 per cent of formic acid was found, and this is probably due to traces of water formed during the ozonisation.

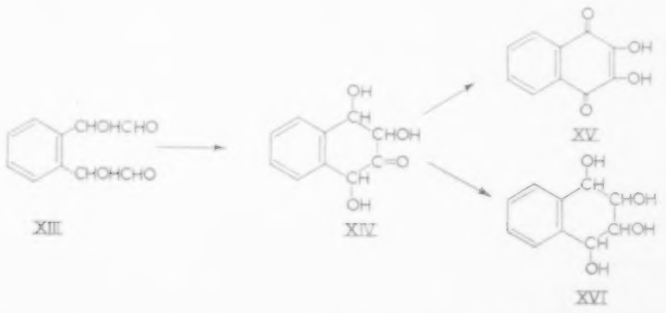
Another explanation may be so-called "anomalous" ozonolysis, which in the literature[21,22] is supposed to occur, if the double bond in question is conjugated with



XII

groups C=O, $-CH_2OH$, —S,— etc. In this case the peroxidic compound would perhaps have a structure as (XII) (or an ionic equivalent) which also could give phenylglyoxal-*o*-carboxylic acid, formic acid and carbon monoxide. Doubts are expressed in the literature, that structures of this type have more than transistory existence except at very low temperatures.

The ozonisation mixture on treatment with sodium iodide in glacial acetic acid, yielded a neutral product, $C_{10}H_{10}O_4$, which reduces Tollens reagent instantly and



XIII XIV XV XVI

Fehlings solution in the cold. It was oxidised to phthalic acid by hydrogen peroxide and reacted with 2:4-dinitrophenylhydrazine to give a mixture of compounds from which only a monohydrazone could be isolated. Likewise only a monourethane was

[21] J. E. Leffler, *Chem. Rev.* **45**, 385 (1949).
[22] R. Criegee, P. de Bruyn and G. Lohaus, *Liebigs Ann.* **583**, 25 (1953).

isolated with phenyl*iso*cyanate. The most probable structure for $C_{10}H_{10}O_4$ is *o*-phenylenediglycolaldehyde (XIII).

A hot alcoholic solution of (XIII) turned intensely violet on addition of potassium cyanide solution. On acidification *iso*naphthazarin (XV) separates. Assuming that (XIII) undergoes an intramolecular benzoin condensation to (XIV) *iso*naphthazarin formation must be accompanied by dehydrogenation. The yield of *iso*naphthazarin under varying conditions, was about one third of the theoretical amount. As a tentative hypothesis, three molecules of (XIV) could yield one *iso*naphthazarin of (XV) and two of hydroxytetralin (XVI) thus:

$$3C_{10}H_{10}O_4 = C_{10}H_6O_4 + 2C_{10}H_{12}O_4$$

The second condensation product has not been isolated.

Since the two C_2-side chains are intact in the reduction product $C_{10}H_{10}O_4$, they must be present in the ozonide which may be represented by (IX). The reduction of the ozonide to $C_{10}H_{10}O_4$ is in itself remarkable since two carbonyls have been reduced to secondary alcohol groups.

The reduction of the ozonide $C_{10}H_6O_5$ to $C_{10}H_{10}O_4$ requires six equivalents of iodide as compared with two equivalents in normal ozonide reductions. Based on the amount of liberated iodine it was found that about 30 per cent of the theoretical amount of ozonide was present immediately after the ozonisation. This is in good agreement with the values for formic acid and carbon monoxide. The amount of $C_{10}H_{10}O_4$ isolated was somewhat higher, about 36 per cent, probably due to contamination with some phenylglyoxal-*o*-carboxylic acid. Analysis for the latter substance, the reduction mixture was found to contain 70 per cent of the theoretical value. Reducing the ozonisation mixture with less than the required amount of sodium iodide necessary for reduction of 30 per cent of the ozonide still gave $C_{10}H_{10}O_4$ but in correspondingly lower yields, and the remainder of the reaction product was again exclusively phenylglyoxal-*o*-carboxylic acid.

Ozonolysis of 1:4-naphthoquinone may proceed via normal or abnormal ozonides but since the content of active oxygen in the reaction mixture decreases very slowly if kept at the same low temperature (−5 to −8°) the interaction between 1:4-naphthoquinone and ozone may be:

(1) 70 per cent of the quinone undergoes anomalous ozonolysis producing free phenylglyoxal-*o*-carboxylic acid and carbon monoxide.

(2) 30 per cent of the quinone converted to the normal ozonide (IX), which slowly rearranges to the mixed anhydride (XI) and decomposes further to (VI) and carbon monoxide.

The rearrangement of the normal ozonide is accompanied by evolution of heat and is not catalysed by *p*-toluenesulphonic acid or acetic acid. The presence of the mixed anhydride (XI) was determined by adding *n*-butyl alcohol to the ozonised solution and distillation of the mixture. An almost quantitative yield of *n*-butyl formate in an azeotropic mixture with *n*-butyl alcohol was obtained.

EXPERIMENTAL

(Melting points are uncorrected.)

Ozone was prepared using an apparatus consisting of ten Berthelot tubes (11000 V). Oxygen was carefully purified and the ozone–oxygen mixture was dried by passing

through a dry ice trap. Chloroform was used as solvent and was purified by distillation from phosphorus pentoxide. A gas washing bottle fitted with a sintered bottom to distribute the gas was used as a reaction vessel.

Ozonisation of 1:4-*naphthoquinone*. A solution of the quinone (5 g) in chloroform (150 ml) was ozonised for 1 hr. The solution lost its yellow colour and acquired a bluish tinge (dissolved ozone). Petrol ether (b.p. 30–40°, 300 ml) was added and the milky suspension chilled in a refrigerator for some hours until a syrup separated. A portion was allowed to decompose in a flask with a suspended strip of filter paper moistened with palladium chloride solution (0·05 mole $PdCl_2$, 0·2 mole Na_2SO_3 and 0·4 mole CH_3COONa). This blackened indicating the presence of CO.

Phenylglyoxal-o-carboxylic acid (VI). On leaving the syrup from the foregoing experiment under the chloroform–petrol ether at +4° for several days the greater part crystallised. In the space above the liquid moist palladium chloride paper rapidly became black. The crystalline substance did not decompose at room temperature and did not liberate iodine from sodium iodide in glacial acetic acid. It was recrystallised twice from glacial acetic acid–carbon tetrachloride (1:1) and from glacial acetic acid. m.p. 120–122° (Found: C, 60·7; H, 3·6; E, 177; $C_9H_6O_4$ requires C, 60·7; H, 3·4%; E, 178). To an aqueous solution of (VI) *o*-phenylenediamine in dilute hydrochloric acid was added when a mass of fine white needles was deposited which crystallised from ethanol, m.p. 277–277·5°. (Found: C, 71·9; H, 4·1; N, 11·2; E, 252. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0; N, 11·2 per cent; E, 250).

Oxidation of phenylglyoxal-o-carboxylic acid to phthalonic acid. The ozonisation mixture from naphthoquinone (5·0 g) was shaken mechanically with water until the chloroform layer gave a negative test with sodium iodide in glacial acetic acid. The aqueous solution was concentrated *in vacuo* to 45 ml. To 30 ml of this solution, concentrated nitric acid (15 ml) was added and the mixture heated on a steam-bath for 5 hr. A viscous yellow oil remained which crystallised on addition of ethanol and stirring (3·3 g), and on recrystallisation from water gave white crystals (0·6 g) m.p. 195° (decomp.) identified as phthalic acid. The mother liquor on concentration gave a yellow oil which slowly crystallised. It was dissolved in ether, filtered, and fractionally precipitated with petrol ether (b.p. 30–40°). The third crop (ether–petrol ether ratio 1:5) gave white crystals m.p. 142–143° (Found: C, 55·9, H, 3·3. Calc. for $C_9H_6O_5$: C, 55·7, H, 3·1 per cent).

Conversion of phenylglyoxal-o-carboxylic acid (VI) *into phthalidecarboxylic acid* (VIII) *and phthalide*. (VI) was sublimed *in vacuo* at 120° (bath temperature). The acid melted and began to froth, and at 132° white crystals appeared on the condenser and the pressure increased from 0·015 mm to 0·075 mm. At 138° the pressure reached 0·12 mm and began to fall as the frothing subsided. The white crystals on the condenser were treated with hot benzine (b.p. 70–80°) leaving a portion undissolved, which was twice recrystallised from ethyl acetate–benzine (1:10) and identified as phthalidecarboxylic acid, m.p. and mixed m.p. with an authentic specimen of (VIII) 155–157°. (Found: C, 60·5, H, 3·6. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·4 per cent). The benzine extract on concentration yielded phthalide m.p. and mixed m.p. with an authentic specimen 69–72°.

Oxidation of acetophenone-o-carboxylic acid with selenium dioxide. To selenium dioxide (0·6 g) in boiling dioxan (10 ml) water was added dropwise until a clear solution was obtained to which acetophenone-*o*-carboxylic acid (1·05 g) was added

and the mixture refluxed for 15 hr. The black precipitate of selenium was removed by filtration, and the solution which only showed a weak reaction for selenium dioxide with aqueous sulphur dioxide, was concentrated to a yellowish brown syrup, which was dissolved in ethanol and filtered to remove traces of selenium. To the ethanolic filtrate *o*-phenylenediamine hydrochloride was added and the crystalline precipitate collected and crystallised from dilute acetic acid. The crystals sintered at 225° and melted at 232°, and mixed with an authentic specimen of the condensation product from phthalonic acid and *o*-phenylenediamine showed no depression. (Found: C, 67·9; H, 4·0; N, 10·4. Calc. for $C_{15}H_{10}O_3N_2$: C, 67·7; H, 3·8: N, 10·5 per cent). Titration of the derivative did not give good values. (Found: E, ca. 250. Calc. E, 266). The end-point (phenolphthalein) was not sharp, probably connected with the fact that the derivative is a hydroxyquinoxaline which can react as a dibasic acid with a second equivalence point at a high pH value.

Hydrolysis of the ozonide of 1:4-*naphthoquinone*. The latter (5 g) was ozonised and the chloroform solution immediately shaken with water (300 ml) until all active oxygen had disappeared. The aqueous layer was distilled and the distillate (250 ml, pH 2–3) was shown to contain formic acid and by titration with standard alkali was found 28 per cent of the theoretical value. If the ozonide solution was left for 5½ hr at room temperature before treatment with water, (all active oxygen having disappeared) alkali titration indicated only 6 per cent of the theoretical value of formic acid.

To determine the amount of phenylglyoxal-*o*-carboxylic acid produced by the hydrolysis of the ozonide, 125 ml of the above-mentioned aqueous layer was treated with *o*-phenylenediamine (1 g) in dilute HCl solution. After 1 hr the derivative was filtered, washed with water and dried to constant weight (1·5 g), corresponding to 95 per cent of the theoretical value. For experimental control phenylglyoxal-*o*-carboxylic acid (0·1014 g) was dissolved in water and precipitated as described above, yielding 0·141 g of derivative, i.e. 99 per cent of the calculated amount.

Quantitative determination of carbon monoxide formed by decomposition of the ozonide. Dry air was passed through the ozonised solution of 1:4 naphthoquinone (2 g) and led through a dry ice trap to remove chloroform and other condensable impurities, and then through a tube filled with granulated iodine pentoxide maintained at 120°. Towards the end of the reaction it was necessary to warm the chloroform. The subsequent procedure is similar to that described by Bayer;[23] 29 per cent of the theoretical amount of carbon monoxide was formed which is high if the 6 per cent formic acid still present in the ozonide mixture after remaining several hours is taken into account.

Only traces of hydrogen peroxide were observed in the ozonised solution after vigorous shaking with ice water for some minutes and addition of potassium titanyl oxalate.

Reduction of 1:4-*naphthoquinone ozonide with sodium iodide*. The ozonised solution of 1:4-naphthoquinone (5 g) was treated with sodium iodide (20 g) in glacial acetic acid. The temperature rose to 30° and the liberated iodine was decolorised with aqueous sodium sulphite and the chloroform layer after washing with water to remove acetic acid was dried over sodium sulphate and evaporated to dryness in a stream of dry air, leaving a residue of brownish oil which crystallised from benzine (b.p.70–80°) and ethyl acetate (2:1) in white needles (0·4 g). The needles were sublimed *in vacuo*

[23] Bayer, "*Gasanalyse*", *Die Chemische Analyse XXXIX* p. 56. Stuttgart (1938).

(0·02 mm) and final crystallisation from ethyl acetate gave white needles m.p. 114–115° (Found: C, 61·4; H, 5·2; $C_{10}H_{10}O_4$(XIII) requires C, 61·8; H, 5·2 per cent). The iodine liberated during reduction of the ozonide was determined by titration with sodium thiosulphate. Based on the oxidation of six equivalents of iodine, the yield of (XIII) corresponded 29·4 per cent of the theoretical value, but the amount of (XIII) isolated as above from the same volume of solution of the ozonide corresponded to 36 per cent.

Excess NaI in the reduction interfered with the isolation of (VI). Reduction with the calculated amount of NaI and conversion of (VI) to the quinoxaline on treatment with *o*-phenylenediamine indicated a yield of 70 per cent. Ozonisation at −60 to −70° (solid CO_2 and acetone) did not increase the content of active oxygen. Reduction of the ozonised solution of naphthoquinone (5 g) with NaI (4 g) in acetic acid (25 ml) and titration with sodium thiosulphate showed that the NaI had been completely oxidised, and the amount of $C_{10}H_{10}O_4$ (crude) was 1·1 g, 18 per cent of the theoretical value. In addition aqueous extracts gave (VI) 85 per cent. To determine the decrease of active oxygen after ozonisation of naphthoquinone (5 g), the solution was kept at −8° and 5 ml samples were withdrawn at intervals (starting from the disappearance of the yellow colour of naphthoquinone) and run unto NaI in glacial acetic acid and titrated with sodium thiosulphate.

Time (hr):	0	1	2	3	4	15
Titration value (ml):	23·3	21·6	21·0	20·3	19·8	16·1

The rate of decrease of active oxygen was not altered significantly by addition of acetic acid or *p*-toluenesulphonic acid. At the ordinary temperature the ozonised solution lost active oxygen in 2 hr.

To a solution of XIII (0·43 g) in hot water (50 ml) hydrogen peroxide (6 ml, 35 per cent) was added, and on evaporation to dryness gave yellowish white crystals (0·31 g, 84 per cent) which were identified as phthalic acid.

2:4-Dinitrophenylhydrazine (1 g) in dilute HCl (110 ml) and XIII (0·23 g) in ethanol (10 ml) gave a red crystalline hydrazone m.p. 164° (decomp). (Found: C, 51·1; H, 3·7; N, 14·6. $C_{16}H_{14}O_7N_4$ requires C, 51·3; H, 3·8; N, 15·0 per cent), corresponding to (XIV). With phenyl*iso*cyanate (2 ml) and triethylamine (2 drops), XIII (0·21 g) in hot benzine (b.p. 90–100°, 10 ml) on refluxing for 30 min deposited white needles, m.p. 144–145° (Found: C, 64·7; H, 5·2; N, 4·4. $C_{17}H_{15}O_5N$ requires C, 65·2; H, 4·8; N, 4·5 per cent), corresponding to addition of XIII (1 mole) and phenyl*iso*cyanate (1 mol).

Intramolecular benzoin condensation of (XIII). To a solution of (XIII) (381 mg) in hot ethanol (5 ml) an aqueous solution of KCN (5 ml, 1 N) was added. The mixture assumed a deep violet colour and after heating (2 min) was acidified with 2 N HCl. After dilution with water (50 ml) and cooling the dark red product was sublimed *in vacuo* and crystallised from benzene, m.p. 276°, and identified as *iso*naphthazarin (XV) (Found: C, 62·9; H, 3·3 Calc. for $C_{10}H_6O_4$ C, 63·2; H, 3·2 per cent) With acetic anhydride a *diacetyl derivative* was obtained, crystallising from aqueous acetone (charcoal), m.p. 110° (Found: C, 61·4; H, 3·8. Calc. for $C_{14}H_{10}O_6$ C, 61·3; H, 3·7 per cent). The identities of *iso*naphthazarin and its diacetyl derivative were established

by comparison of their X-ray powder diagrams with those of authentic samples. Some examples of the yield of condensations and the conditions are given below.

$C_{10}H_{10}O_4$(mg)	Ethanol	KCN	Boiling	Yield (mg)	
645	15 ml	10 ml, 1 N	1 min	235	
2000	20 ml	0·5 g, 10 ml H_2O	1 min	650	(hydrogen
282	3 ml	0·1 g, 100 ml H_2O	5 min	100	atm).

Existence of the mixed anhydride (XI). To the ozonised solution of naphthoquinone (10 g) in chloroform (250 ml) pure *n*-butyl alcohol was added in 30 min and the temperature rose to 35°. Distillation of the mixture through a Widmer column gave a fraction (3·23 g, b.p. 102–106°), and the hydrolysis indicated 2·07 g (32 per cent) *n*-butyl formate. Refractionation gave the azeotrope (b.p. 105–106°) with an ester content of 76 per cent. The binary azeotrope of *n*-butyl formate and *n*-butyl alcohol is reported[24] to have b.p. 105·8° and an ester content of 76·4 per cent. The identity of the azeotrope was established by comparison of its infra-red spectrum with that of an authentic sample.

[24] Hannotte, *Bull. Soc. Chim. Belg.* **35**, 90 (1926).

Tetrahedron, 1958, Vol.4, pp. 223-240. Pergamon Press Ltd., London

SYNTHESIS OF IPECACUANHA ALKALOIDS*

R. P. EVSTIGNEEVA and N. A. PREOBRAZHENSKY
The Lomonosov Institute of Fine Chemical Technology, Malaya
Pirogovka 1, Moscow

(*Received* 10 *April* 1958)

Abstract—Alkaloids of ipecacuanha are plant bases of a complex chemical structure. The structures of emetine and related alkaloids have been extensively studied. This paper summarises the work carried out by the present authors in the course of many years and deals with the procedures of building up particular groups characteristic of these alkaloids and their parent substances. The investigation has led to the assignment of the structures and to the syntheses of isomeric and stereoisomeric emetines and related alkaloids such as O-methylpsychotrines, psychotrine, cephaeline, emetamine and a number of their analogues. The syntheses of alkaloids of the *iso*quinoline, quinoline, and indole series have been shown to be interconnected and have been effected from the same parent compounds and by similar conversions.

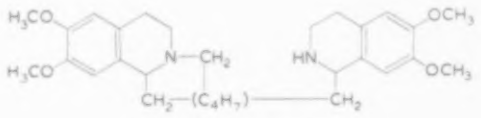
ALKALOIDS of the *iso*quinoline group are of great theoretical and practical interest, including a number of important compounds widely used in medicine, such as morphine and related alkaloids, *d*-tubocurarine and many others. The study of the chemical structure and conversions of *iso*quinoline alkaloids was therefore deemed to be of great theoretical value, and it has helped to establish a genetic and chemical relationship between alkaloids of different groups, for example, between the derivatives of *iso*quinoline, quinoline and indole.

A group of chemically related alkaloids produced from the tropical plant Ipecacuanha, namely emetine, O-methylpsychotrine, psychotrine, cephaeline and emetamine are *iso*quinoline derivatives.

Synthesis of isomeric and stereoisomeric emetines

Emetine was first discovered in 1817[1] and in 1879 Podvisotsky obtained it as a pure substance;[2] its empirical formula was only established in 1914, because of the extremely complicated procedure involved in purifying the alkaloid. The crystalline base of emetine was not produced until 1953.[3]

The study of various reactions of emetine carried out by several investigators showed that its molecule consists of two tetrahydro*iso*quinoline nuclei linked by a group of seven carbon atoms.



I

The further elucidation of the structure of emetine proved to be very difficult. The suggested formulae did explain many emetine reactions, but none of them fully accounted for its properties.

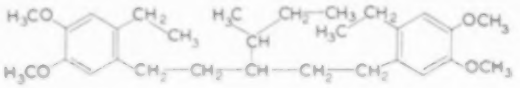
* Translated by A. L. Pumpiansky, Moscow.

[1] J. Pelletier and Magendie, *Ann. Chim. Phys.* [2], **4**, 172 (1817).

[2] V. Podvisotsky, New pharmacological and chemical investigations of the ipecacuanha root alkaloid emetine. (1879).

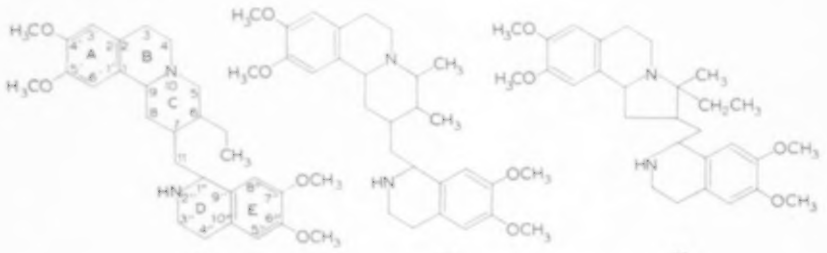
[3] G. E. Foster and G. W. Nargrove, *J. Pharm. Pharmacol.* **5**, 480 (1953).

In 1948–1950 many investigations were published of attempts to elucidate the structure of the central part of the emetine molecule.[4] The products of degradation of emetine, produced by exhaustive methylation, were investigated and synthesised, and many compounds derived from emetine and other related alkaloids were obtained. These investigations determined the structure of the hydrogenated product obtained by exhaustive methylation of emetine (II) that fully retained the nitrogen-free alkaloidal skeleton.



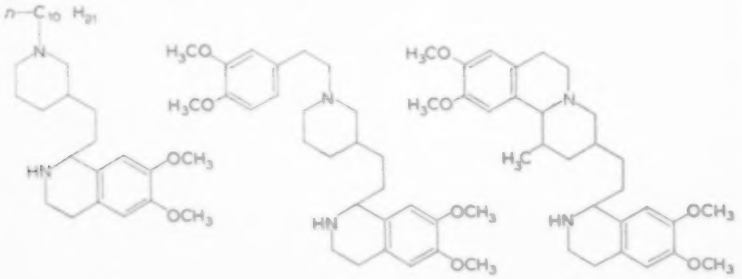
II

This structure suggested three probable formulae of emetine, namely (III), (IV) and (V), as shown:



III IV V

On the basis of investigations of *iso*quinoline compounds with structures close to that expected for emetine such as 1-β-[(*N*-decyl)-3′-piperidyl]ethyl-6:7-dimethoxy-1:2:3:4-tetrahydro*iso*quinoline[5] (VI), 1-β-[*N*-β-(3″:4″-dimethoxyphenyl)ethyl-3′-piperidyl] ethyl-6:7-dimethoxy-1:2:3:4-tetrahydro*iso*quinoline[6] (VII), 1″-(4′:5′-dimethoxy-8-methyl-3:4:5:6:7:8-hexahydrobenzo-1′:2′:1:2-quinolizine-6-ethyl)-6″:7″-dimethoxy-1″:2″:3″:4″-tetrahydro*iso*quinoline[7] (VIII)



VI VII VIII

[4] E. Späth and M. Pailer, *Mh. Chem.* **78**, 348 (1948); M. Pailer and L. Bilck, *Mh. Chem.* **79**, 127 (1948); M. Pailer, *Mh. Chem.* **79**, 331 (1948); M. Pailer and K. Porschinski, *Mh. Chem.* **80**, 94 (1949).

[5] R. S. Livshits, M. S. Bainova, S. D. Kuprianova and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXIII**, 522 (1953).

[6] R. S. Livshits, M. S. Bainova, A. J. Gurevich and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXIII**, 525 (1953).

[7] R. P. Evstigneeva, Dissertation "The Synthesis of the alkaloid emetine" (1950); L. I. Zakharkin and N. A. Preobrazhensky. *Zh. Obshch. Khim.* **XXIII**, 153, 518 (1953).

Formula (III) was postulated as the most probable for the alkaloid and a synthetical investigation was made.

Robinson came to this conclusion, starting from the structural and genetic relationship of the alkaloids of the *iso*quinoline group.[8]

Emetine was found to have the postulated structure (III), since the destructive degradation of emetine resulted in the isolation of the central part of the molecule as β-ethyl-γ-methylpyridine. Final confirmation of the emetine structure was obtained by the synthesis effected in 1950.[9]

Several routes were studied as shown in the general scheme (see p. 226):

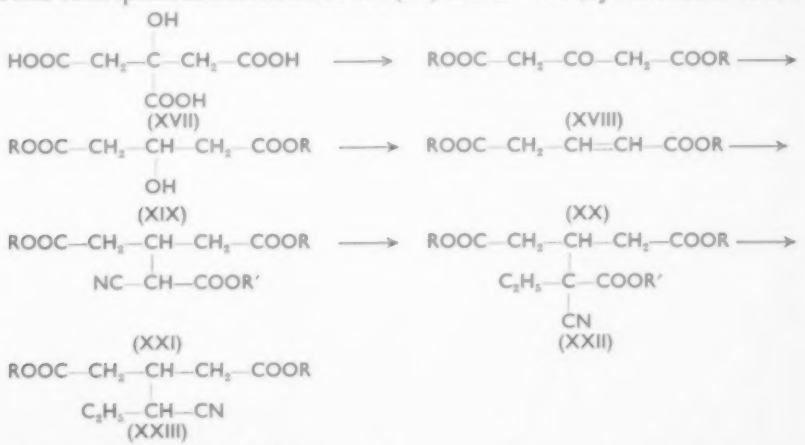
It was decided to make use of a starting compound whose structure would predetermine the structure of the whole central part of the alkaloid molecule, that is, of that part of the molecule requiring experimental evidence. The structure of this parent compound corresponded to the general formula (IX). There being the necessary and suitably arranged functional groups —COOR, $-CH_2Br$, $-CH(OR)_2$ and —CN in the structure (IX), the condensation of this compound with homoveratrylamine permitted the building up of the quinolizine and *iso*quinoline systems involved in the structure of emetine. As starting substances for the central part of the emetine molecule, the following compounds were synthesised:

(a) ethyl β-(α'-bromomethyl)propylglutarate (IX; Z = CH^2Br);[10] m.p.132·5–133·5°

(b) β-(α'-diethylacetal)propylglutaric acid anhydride (IX, Z = $-CH(OC_2H_5)_2$);[11] b.p. 155–157°/4 mm.

(c) methyl and ethyl β-(α'-cyano)propylglutarates (IX; Z = CN).

The compound that proved to be the most convenient for synthesising emetine, its isomers and other ipecacuanha alkaloids was (IX) with Z = CN, synthesised as follows:

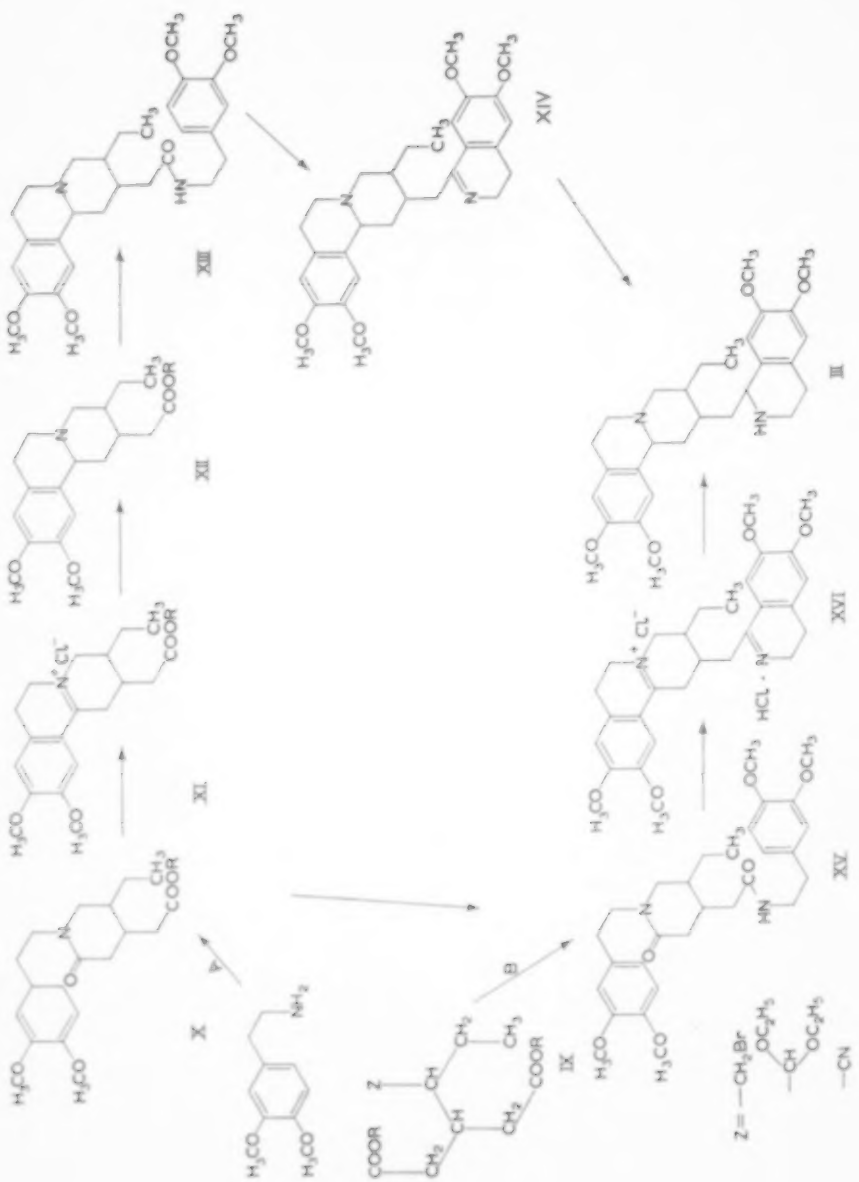


[8] R. Robinson, *Nature, Lond.* **162,** 155 (1948).

[9] R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova and N. A. Preobrazhensky, *Dokl. Akad. Nauk. SSSR* **75,** 539 (1950); *Zh. Obshch. Khim.* **XXII,** 149 (1952).

[10] L. I. Zakharkin and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXII,** 1890 (1952).

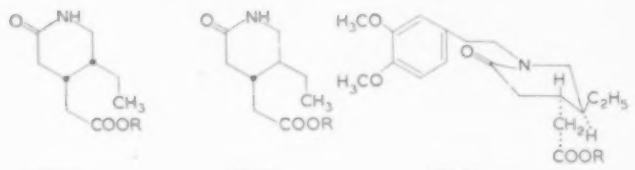
[11] M. S. Bainova, R. P. Evstigneeva, R. S. Livshits, K. K. Kusmina and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXIII,** 149 (1953).



The chief intermediate used in the syntheses was ethyl glutaconate (XX; R = CH_3, C_2H_5), obtained from citric acid (XVII) via acetonedicarboxylic acid (XVIII; R = H), its esters (XVIII; R = CH_3, C_2H_5), ethyl and methyl β-hydroxyglutarates (XIX; R = CH_3, C_2H_5) and ethyl and methyl β-acetoxyglutarates. The glutaconates were condensed with ethyl cyanoacetate to give (XXI; R = R′ = C_2H_5), b.p. 182–183°/3 mm, and (XXI; R = CH_3, R′ = C_2H_5), 158–159°/2 mm. After alkylation of (XXI) with ethyl halide we obtained (XXII; R = R′ = C_2H_5), b.p. 189–190°/3 mm, (XXII; R = CH_3, R′ = C_2H_5), (XXI; R = CH_3, R′ = C_2H_5), b.p. 156–158°/1 mm, and (XXII; R = R′ = CH_3), b.p. 150–152°/1 mm.

The selective saponification of one of the ester groups to (XXII) followed by decarboxylation resulted in (XXIII; R = C_2H_5), b.p. 139–140°/2·5 mm, (XXIII; R = CH_3), 126·5–127°/1 mm. The reductive condensation of (XXIII) with homoveratrylamine (route A) in the presence of Raney nickel led to the addition of the latter compound to the nitrile group accompanied by the elimination of ammonia.

Simultaneously, the secondary amino group produced reacted with one of the carboalkoxy groups to yield ethyl and methyl *N*-(β-(3′:4′-dimethoxyphenyl)-ethyl)-δ-ethyl-α-piperidone-γ- acetates (X; R = C_2H_5 and R = CH_3), b.p. 200·5–202·5°/0·15 mm and 210–211°/0·35 mm, respectively. With the main reaction a side-reaction took place to give non-alkylated piperidones (XXIVa), (XIVb) and dihomoveratrylamine.



XXIVa XXIVb XXV

The usual ratio of alkylated to non-alkylated piperidones was 6:1 or 5:1. The yield of alkylated piperidone amounted to about 30 per cent. Piperidone (XXIV) was isolated in two stereoisomeric forms (a and b). Piperidone (X) should also have two isomeric forms, but all attempts to isolate the second isomer in a pure state failed. The substituent at the nitrogen seemed to favour the formation of one isomer only. As far as conformational analysis was concerned, the most favourable transform for the N-substituted piperidone (X) was apparently that with equatorial substituents (XXV).

Piperidone (X) was then cyclised to the chloride of the quaternary base (XI), with phosphorus oxychloride, pentachloride and pentoxide used as reagents. The further reduction of (XI) led to ethyl and methyl 4′:5′-dimethoxy-6-ethyl-3:4:5:6:7:8-hexahydrobenzo-(1:2:1′:2′)-quinolisyl-7-acetates (XII).

Hydrogenation of the chloride of the quaternary base (XI) was stereo-oriented, depending on the catalyst and the pH of the medium used. The above described synthesis resulted in the following three isomeric quinolizine esters[12]:

(*A*) An isomer with the melting point of the amorphous hydrochloride 177·5–179·5° and that of the crystalline hydrate 195–196°, obtained on hydrogenation in the presence of platinic oxide in acidic media (XII; R = C_2H_5).

[12] R. P. Evstigneeva, *Zh. Obshch. Khim.* **XXVIII**, 2458 (1958).

(*B*) An isomer with the melting point of its amorphous hydrochloride. 171·5–173·5° and that of the crystalline hydrate 194–196°, produced when hydrogenating in the presence of platinic oxide in neutral media (XII; $R = C_2H_5$).

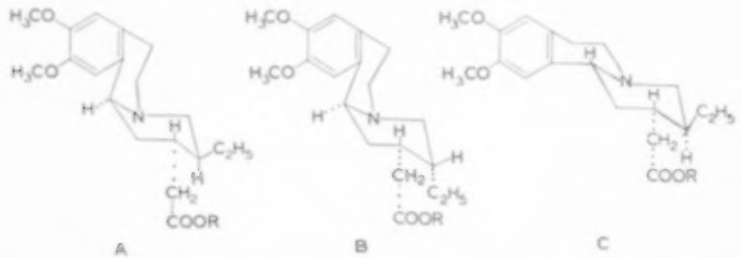
(*C*) An isomer with the melting point of its amorphous hydrochloride 175–179° and that of its crystalline hydrate 193·5–194·8°, obtained by hydrogenation in the presence of Raney nickel in neutral media (XII; $R = C_2H_5$).

It is to be noted that the esters of the quinolizine derivative of (XII) are extremely difficult to investigate.

The bases are isolated as oils. The salts of the anhydrous base with mineral and organic acids are amorphous. The isomeric esters have been identified as hydrochlorides, then converted into crystalline hydrates by adding a small amount of hydrochloric acid, followed by careful removal of the latter *in vacuo* and recrystallisation from alcohol.

The isomers produced are very similar in properties, but exhibit sharp depression of the mixed melting point of their hydrochlorides. Their ultra-violet absorption spectra proved to be almost identical.

The isomers appear to have the following configurations:



Hydrogenation with nickel catalyst proceeds with isomerisation also observed in distilling unstable bases of (XII). Heating with homoveratrylamine at 180–200° converts the stereoisomeric quinolizine esters (XII A), (XII B) and (XII C) into their respective amides with very similar properties, m.p. 144–145° (XIII A), 147·5–148·5° (XIII B) and 144–146·5° (XIII C), but showing depression of their mixed melting points.

Amides (XIII A), (XIII B) and (XIII C) when treated with phosphorus oxychloride gave *iso*quinoline derivatives with the composition and structure corresponding to those of the O-methylpsychotrine alkaloid.[13]

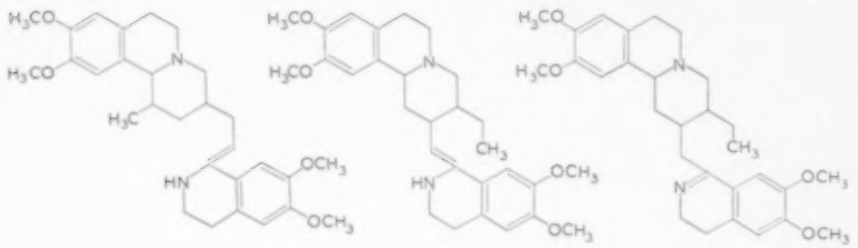
The bases of (XIV) were isolated as amorphous substances, m.p. 59–60° (XIV A), 58–59° (XIV B) and 58–59° (XIV C), unstable when exposed to atmospheric oxygen or sunlight. Their oxalates were isolated as readily crystalline hydrates with melting points coinciding, namely with (XIV A), 145·5–147° (dec.), with (XIV B), 146·5–148° (dec.), and with (XIV C), 145·5–147·5 (dec.). The (±)-tartrates crystallise as anhydrous compounds melting at 123–125° (XIV A), 125° (XIV B) and 160° (XIV C).

The N-acetyl-O-methylpsychotrines have also been prepared, their bases being isolated as colourless amorphous substances, m.p. 78–79° (XIV A), 98–99° (XIV B) and 73–74° (XIV C), and their oxalates, m.p. 147–148° (dec.) in the case of (XIV A), 152° (dec.) of (XIV B), and 151° (dec.) of (XIV C).

[13] R. P. Evstigneeva, R. G. Glushkov and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXVIII**, 2463 (1958).

All bases, oxalates and (+)-tartrates of O-methylpsychotrines as well as the bases and oxalates of N-acetyl-O-methylpsychotrines show a depression of the mixed melting point.

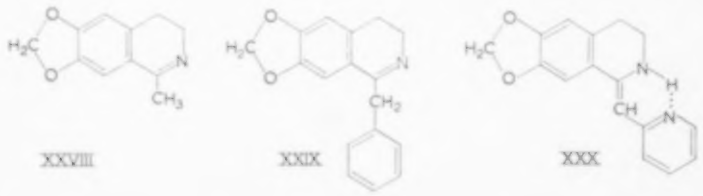
The ipecacuanha alkaloid O-methylpsychotrine was first discovered in 1917. It differs from emetine in having two hydrogen atoms less and can be obtained from the latter on oxidation with mercuric acetate. It was referred to as a secondary–tertiary base, since, when heated with benzoic anhydride, it gives a monosubstituted N-benzoyl derivative. In 1927, in accordance with one of the structures suggested for emetine, it had been assigned the following formula (XXVI):[14]



XXVI XXVII XIV

The position of the double bond was confirmed by the fact that the N-benzoyl-O-methylpsychotrine on oxidation with perphthalic acid and ozone yields N-benzoyl-corydaldine.[15]

In 1949, on the basis of the structure of emetine, O-methylpsychotrine was assigned formula (XXVII), but more recent investigations of the ultra-violet absorption spectrum of O-methylpsychotrine have led to the conclusion about the double bond in the dihydro*iso*quinoline ring being in the 1:2-position (XIV).[16] This suggestion being, however, hardly compatible with the secondary–tertiary character of the base, the structure of O-methylpsychotrine still remained doubtful. The position of the double bond in the 3:4-dihydro*iso*quinoline ring was uncertain not only for O-methyl-psychotrine but for a whole group of similar compounds as well. Having studied the ultra-violet absorption spectra of 1-methyl-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (XXVIII), 1-benzyl-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (XXIX) and 1-(α-picolyl)-3:4 dihydro-6:7-methylenedioxy*iso*quinoline (XXX), and having compared them with those of stilbene and α-stilbazole, Bills *et al.*[17] suggested the exocyclic position of the double bond in (XXX) and the endocyclic one in (XXVIII) and (XXIX).

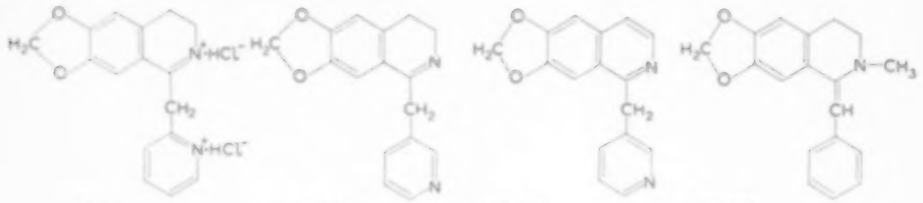


XXVIII XXIX XXX

[14] W. H. Brindley and F. L. Pyman, *J. Chem. Soc.* 1067 (1927).
[15] P. Karrer, C. H. Eugster and O. Rüttner, *Helv. Chim. Acta* **31**, 1219 (1948).
[16] H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.* 391 (1952).
[17] J. L. Bills, C. R. Noller and M. Axima, *J. Amer. Chem. Soc.* **72**, 17 (1952).

During the conversion from base (XXX) to the hydrochloride (XXXI) the character of the absorption curve changes, apparently owing to the rearrangement of the double bond in the ring. The exocyclic structure of compound (XXX) seems to be accounted for by the possibility of the intramolecular hydrogen bond formation. This is confirmed by 1-(β-picolyl)-3:4-dihydro-6:7-methylendioxy*iso*quinoline (XXXII), which has no intramolecular hydrogen bond, having an endocyclic double bond, as shown by the absorption spectra and the conversion of (XXXII) into the *iso*quinoline derivative (XXXIII).

On the other hand, 1-(α-picolyl)-3:4-dihydro-6:7-methylenedioxy*iso*quinolien (XXX) gave no *iso*quinoline derivative.



XXXI XXXII XXXIII XXXIV

The investigations suggested that the position of the double bond for 1-substituted-3:4-dihydro*iso*quinoline compounds is endocyclic, and only in few cases is the exocyclic position possible.

Openshaw and Wood, comparing the ultra-violet data of the natural O-methylpsychotrine oxalate with those of 1-methyl-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (XXVIII.HCl) came to the conclusion that the double bond in O-methylpsychotrine was endocyclic. Although this conclusion is ultimately correct, it cannot be arrived at solely in terms of the spectrum of the salt, since it is also necessary to have the spectral data concerning the base, as it is possible for the salt and the base to have a different position of the double bond.

We have therefore undertaken the spectral investigation of stereoisomeric synthetic O-methylpsychotrine oxalates. The ultra-violet absorption curves of the three isomers were found to coincide with and to be similar to that of the natural O-methylpsychotrine oxalate, which is also so for the spectra of (+)-O-methylpsychotrine tartrate.

We have also investigated the ultra-violet data concerning O-methylpsychotrine bases produced from purified oxalates. The absorption curves of the bases proved to be similar and their maxima situated similarly to those of the absorption curves of 1-methyl- and 1-benzyl-3:4-dihydro-6:7-methylenedioxyquinolines [(XXVIII) and (XXIX)]. Correspondingly, the structure of O-methylpsychotrine should be given by the formula (XIV) with an endocyclic bond.

It is known that O-methylpsychotrine yields monoacyl derivatives in which the double bond can be only exocyclic. N-Benzoyl- and N-succinyl-O-methylpsychotrines resulting from the natural O-methylpsychotrines are described in the literature. The N-acetyl derivatives of stereoisomeric O-methylpsychotrine have been obtained. The bases of N-acetyl-O-methylpsychotrines are more stable to light, the atmosphere and other influences. If O-methylpsychotrine is dissolved in carbon tetrachloride the solution becomes opaque, in 15–20 min, a red precipitate, m.p. 171–178° (164°), being produced. On the other hand, N-acetyl-O-methylpsychotrine base when dissolved in

carbon tetrachloride results in a clear solution, which remains unchanged for several days. The ultra-violet spectra of N-acetyl-O-methylpsychotrine bases and their oxalates proved respectively to be similar to those of O-methylpsychotrines, which is also so with 1-benzylidene-1:2:3:4-tetrahydro-2-methyl-6:7-methylenedioxy*iso*quinoline (XXXIV).

Ultra-violet data are thus not reliable enough to serve as a means of determining the position of the double bond.

Infra-red data provide in many cases better results. With O-methylpsychotrine the position of the double bond should be easily determined by making use of infra-red spectra as in the case of an exocyclic double bond present the molecule must involve the N—H group with a definite characteristic infra-red absorption band over the range 3500–3100 cm^{-1} (2·86–3·23 μ). The infra-red spectrum of the O-methylpsychotrine base (in petroleum jelly) shows no absorption bands at this frequency, thereby denoting the absence of the exocyclic double bond. The spectrum of the O-methylpsychotrine base in carbon tetrachloride also revealed the absence of the N—H group. The spectrum of a reference substance, dihomoveratrylamine, at the same concentration shows the band of the N—H group at 3293·5 cm^{-1}, indicating the presence of an intramolecular hydrogen bond. To investigate the hydrogen bond it is customary to substitute deuterium for hydrogen, and this often results in a sharp displacement of the characteristic frequency to a longer wavelength. We have attempted by this procedure to find the N—H group in O-methylpsychotrine. The deuterium–hydrogen exchange is known to proceed extremely readily in the alcoholic and amino groups,[18] whilst that of hydrogen linked with carbon does not take place at all under ordinary conditions.[19] The O-methylpsychotrine base was dissolved in dry dioxane and an excess of heavy water was added. After standing for 2 days the base was isolated and spectroscopically investigated. The N–D band has not been found, denoting the absence of an exocyclic bond in O-methylpsychotrine. With dihomoveratrylamine deuterium–hydrogen exchange did not take place. This is in accordance with other known facts of hindered hydrogen exchange when hydrogen is present in the intramolecular hydrogen bond. For example, hydrogen does not exchange in 1-hydroxyanthraquinone[20] or 1-benzeneazo-2-naphthylamine.[21] Thus the infra-red spectra of O-methylpsychotrine base indicated the presence of the endocyclic double bond. Spectroscopic investigation of O-methylpsychotrine was extremely complicated owing to the presence of water of crystallisation. On the basis of spectroscopic data in the 1200–1700 cm^{-1} region the absence of N–H group in the salt is definite.

The structure of O-methylpsychotrine therefore corresponds to formula (XIV). The formation of mono-N-acyl derivatives may be accounted for by tautomerism with a preferential shift to the compound with the endocyclic double bond (XIV).

The exocyclic position of the double bond (prototropic rearrangement) is due to the influence of alkali and is retained by the acylating agent.

The final step in the synthesis of emetine consists in the reduction of *O*-methylpsychotrine effected both catalytically and chemically. The reduction of the natural

[18] J. Hine and C. H. Thomas, *J. Amer. Chem. Soc.* **75**, 730 (1953); *Ibid.* **76**, 612 (1954); H. Kwart, L. P. Kuhn and E. L. Bannister, *J. Amer. Chem. Soc.* **76**, 5998 (1954).

[19] D. N. Kursanow, V. N. Setkina and A. P. Mestcher'akov, *Dokl. Akad. Nauk SSSR* **105**, 279 (1955); A. I. Shatenshtein, K. I. Zhdanova, L. I. Vinogradov and V. R. Kalinatchenko, *Dokl. Akad. Nauk SSSR* **102**, 779 (1955).

[20] D. N. Shigorin and N. S. Dokunikhin, *Dokl. Akad. Nauk SSSR* **100**, 323 (1955).

[21] G. D. Bagratishvili, *Dokl. Akad. Nauk SSSR* **96**, 753 (1954).

O-methylpsychotrine with sodium in alcohol results in a mixture of emetine and *iso*-emetine. The catalytic hydrogenation is stereo-oriented.

Taking into consideration the main conformational positions available for emetine, it is possible to formulate eight most stable conformations and these correspond to the number of racemic isomers of the alkaloid in terms of the classical theory.

Four of these conformations have the rings B and C linked in the *trans* position and the other four in the *cis*-position. The large substituents are situated equatorially.

The carbon–carbon linkages at C_7 and C_1 are only equatorial, this being achieved by allowing for the conversion of ring D. The above conformational formulae of emetine seem to be the most plausible ones. The possibility of the existence of other isomeric forms must not be excluded, e.g., those with polar substituents at C_7 and C_1. The conformation of (—)-emetine (natural) should be expressed by one of the structures. In accordance with recent investigations[22] dealing with emetine stereochemistry, the natural alkaloid would be in α-conformation. This conclusion must however be considered as tentative, the absolute configuration at C_1 not having been determined.

In attempting to find suitable routes to synthesise (—)-emetine (natural), each of the isomeric O-methylpsychotrines was reduced with hydrogen under three different conditions: (a) in the presence of platinic oxide in acidic medium, (b) in the presence of platinic oxide in ammonia–alkali medium and (c) with Raney nickel in neutral medium.

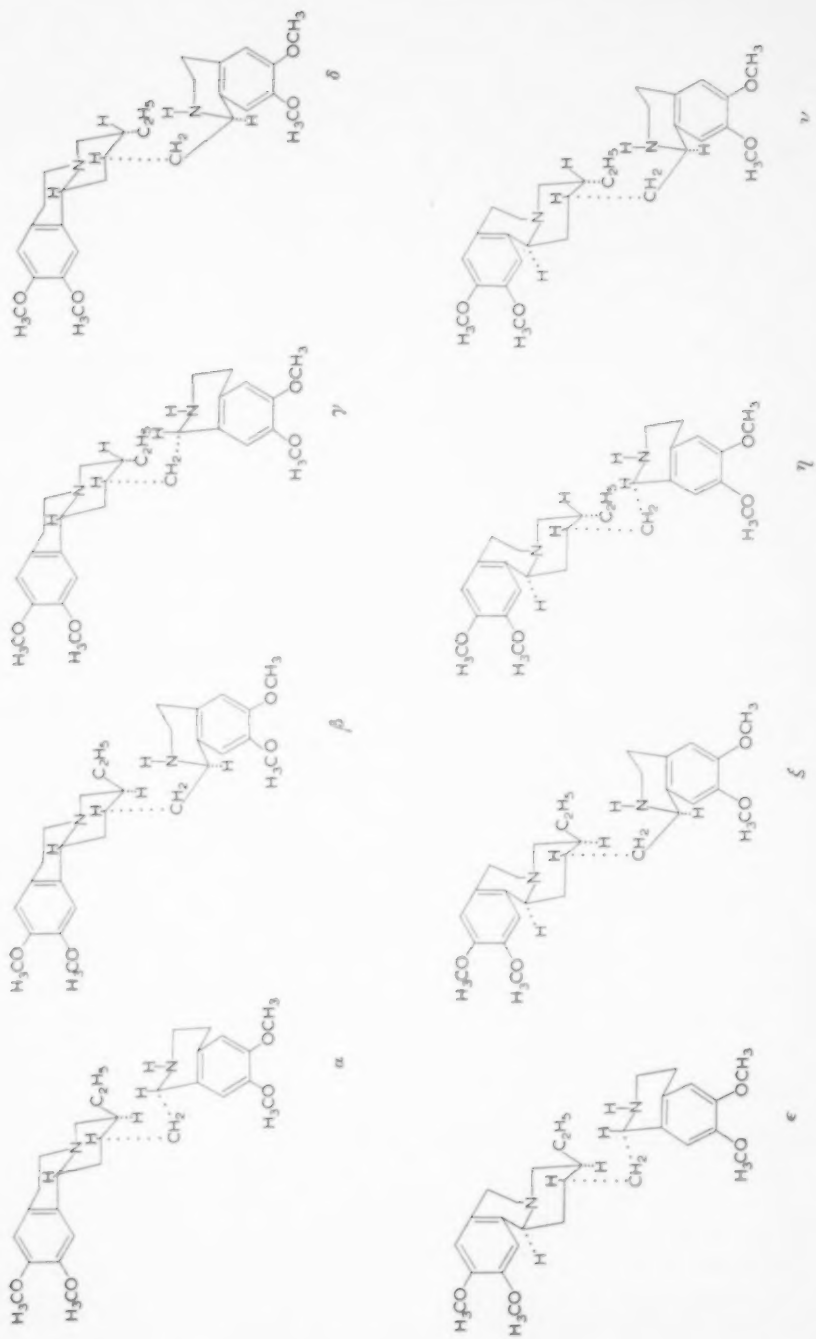
For convenience each emetine is designated by two signs, the first denoting the conditions of the hydrogenation of the quaternary chloride of the quinolizine derivative of (XI), the second one characterising conditions of the hydrogenation of the 3:4-dihydro*iso*quinoline nucleus of O-methylpsychotrine. We have thus obtained eight isomeric substances: 1, AB; 2, AA; 3, AC; 4, BB; 5, BA; 6, BC; 7, CC and CB; 8, CA.

Emetine has also been produced via a shortened synthetic route (B) through the diamide (XV) with a simultaneous closure of two *iso*quinoline rings (XVI) and hydrogenation of two double bonds (III) in the presence of Raney nickel.

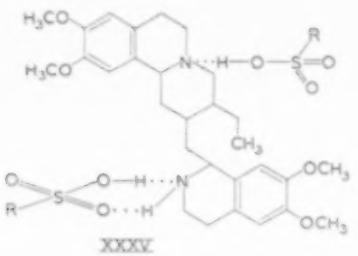
Hydrogenation of O-methylpsychotrines proceeds in all cases in nearly quantitative yield, the bases being isolated as oily or amorphous substances. Anhydrous hydrates are also amorphous, readily absorb moisture in the air and give crystalline hydrates which are not suitable for comparing isomeric compounds, as they lack sharp melting points and anhydrous salts of emetine are very hydroscopic, the drying of emetine being rather difficult because it is often accompanied by change in the substance. Crystalline salts of (—)-emetine with mineral acids described in the literature appear only as hydrates. We have obtained a number of salts of (—)-emetine with organic acids, the most striking being the camphor-β-sulphonates, which readily crystallise without hydrate formation.

The (±)-camphor-β-sulphonate of (—)-emetine was investigated as regards infra-red spectra. For comparison the infra-red spectra of the (—)-emetine base and (±)-camphor-β-sulphonic acid were taken, the former distinctly revealing the absorption band of the non-associated N–H group at 3371 cm^{-1}. The spectrum of (—)-emetine

[22] A. R. Battersby, R. Binks, D. Davidson, G. C. Davidson and T. P. Edwards, *Chem. & Ind.* 982 (1957); A. R. Battersby and S. Cox, *Chem. & Ind.* 983 (1957); E. van Tamelen, P. E. Aldrich and J. B. Hester, *J. Amer. Chem. Soc.* **79**, 4817 (1957).


δ
ν
γ
η
β
ζ
α
ε

(±)-camphor-β-sulphonate shows three new bands that can be referred to salt formation (2512, 2556 and 2600 cm^{-1}). On comparing it with the infra-red absorption-spectra of (±)-camphor-β-sulphonates of aniline, pyridine and piperidine, (−)-emetine (±)-camphor-β-sulphonate was found to represent a complex compound involving one molecule of the base and two of (±)-camphor-β-sulphonic acid linked with hydrogen.



XXXV

The (+), (−) and (±)-camphor-β-sulphonic acids were used to obtain salts for the investigation of synthetic isomeric emetines.

The reaction of emetine bases with (+)-, (−)- and (±)-camphor-β-sulphonic acids in alcoholic solution gives crystalline salts. Isomeric camphor-β-sulphonates are very similar as regards melting points, but differ in solubility in ethanol. Their mixed melting points all show a depression, except those of the respective camphor-β-sulphonates CC and CB. The ultra-violet spectra of (±)-camphor-β-sulphonates are similar with the same maxima (235 mμ and 285 mμ) and minimum (255 mμ), but slightly different in the intensity of the first maximum and minimum. The emetine bases derived from crystalline camphor-β-sulphonates have very similar melting points, that is: 1, 74–75° (60°); 2, 71·5–72° (68°); 3, 72·5–73° (67°); 4, 70–71° (66·5°); 5, 68–70° (65°); 6, 74–75° (65°); 7, 73·5–74·5° (70°); 8, 95–96° (73°); but they show a depression of their mixed melting points. For example, the mixture of emetine bases 7, CB, and 8, CA, melts at 50° with deformation, softens at 59° and forms a meniscus at 84°. Difficulty is experienced in determining the mixed melting points, since the emetine bases are more readily electrified than the camphor-β-sulphonates when ground. After the separation of crystalline (+)-camphor-β-sulphonates about 50 per cent of salt remains in the alcoholic mother-liquor and is not precipitated even after prolonged standing in the cold, and other solvents also proved to have little effect, and the free bases were isolated to obtain oxalates. The latter contain water of crystallisation (about 1 molecule) and melt at: 1, 166° (152°); 2, 167–168° (156°); 3, 166° (157°); 4, 154° (148°); 5, 158° (140°); 6, 166° (161°); 7, 166–167° (156°); 8, 177–178° (156°); their ultra-violet spectra are also nearly similar. The oxalates yielded bases melting at: 1, 73–74° (60°); 2, 71–71·5° (68°); 3, 72·5–73° (65°); 4, 70–71° (65°); 5, 68–70° (65°); 6, 74–75° (65°); 7, 73·5–74·5° (70°); 8, 95–96° (73°); their properties were similar to those of the natural alkaloid. The melting points, ultra-violet spectra and rotation of the base and oxalate of isomer CC proved to be identical with those of the natural alkaloid. Several (−)-emetine salts have been obtained, namely, (+)-camphor-β-sulphonate of emetine, $C_{29}H_{40}O_4N_2.2C_{10}H_{16}O_4S$, m.p. 229–231·5°, $[\alpha]_D^{20°}0°$(*c*, 7·46 in water), isolated from alcohol as fine plates or needles; (+)-camphor-β-sulphonate of (−)-emetine, $C_{29}H_{40}O_4N_2.2C_{10}H_{16}O_4S$, m.p.

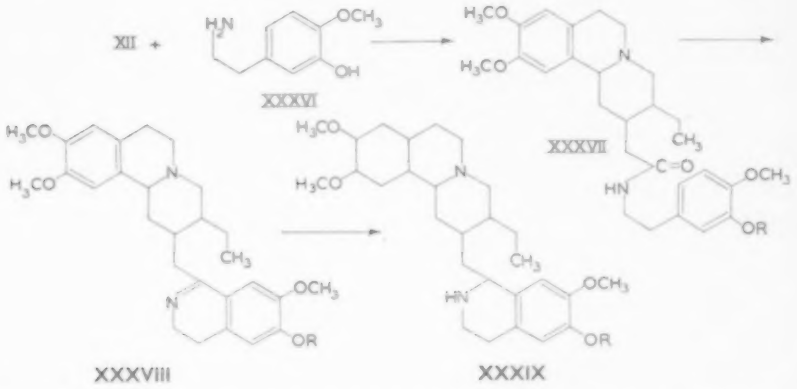
215° (212°), $[\alpha]_D^{20°}$ + 13·85° (*c*, 8·77 in water), isolated from acetone as fine plates; (−)-camphor-β-sulphonate of (−)-emetine, $C_{29}H_{40}O_4N_2.2C_{10}H_{16}O_4S$, m.p. 235·8–236·5° (223°), $[\alpha]_D^{15·5°}$ −8·4° (*c*, 8·43 in water), isolated from water as long tetragonal prisms; (+)-tartrate of (−)-emetine $C_{29}H_{40}O_4N_2.2C_4H_6O_6$, m.p. 159–161·5°, 170° (dec.), $[\alpha]_D^{15·5°}$ + 16·2° (*c*, 7·29 in water), isolated from alcohol as an amorphous substance; (−)-tartrate of (−)-emetine, $C_{29}H_{40}N_2O_4.2C_4H_6O_6.\frac{1}{2}H_2O$, m.p. 155° and 172° (dec.), $[\alpha]_D^{13·5°}$ 0°(*c*, 5·14 in water), isolated from alcohol as an amorphous substance.

Oxidation of the synthetic base of (−)-emetine with iodine resulted in rubremetinium iodide similar in properties to that produced from the natural alkaloid.

Synthesis of phenolic bases of ipecacuanha alkaloids of psychotrine and cephaeline

The phenolic bases of ipecacuanha (+)-psychotrine and (−)-cephaeline are derived from the plant in minute quantities and are very difficult to purify.

The syntheses of (±)-psychotrine (XXXVIII; R = H), (±)-cephaeline (XXXIX; R = H) and their derivatives have been effected following the scheme elaborated for emetine:



The methyl 4′:5′-dimethoxy-6-ethyl-3:4:5:6:7:8-hexahydrobenzo-(1:2:1′:2′)-quinolizyl-7-acetate (XII; R = CH_3) was obtained following the procedure described above, with Raney nickel to reduce the quaternary chloride. The melting temperature of the hydrochloride (crystalline hydrate) was 195–195·5°. β-(3-Hydroxy-4-methoxyphenyl)ethylamine was obtained selectively by demethylating homoveratrylamine with metallic sodium in liquid ammonia,[23] m.p. 147–148°; the hydrochloride melted at 204–206°. Condensation of (XII) with β-(3-hydroxy-4-methoxyphenyl)ethylamine (XXXVI) resulted in the hydroxyamide (XXXVII, R = H), m.p. 101–102°. By reaction with benzyl chloride this hydroxyamide gave the corresponding O-benzyl derivative (R = $CH_2C_6H_5$), m.p. 106–107°, which on being cyclised with phosphorus oxychloride gave O-benzylpsychotrine (XXXVIII), R = $CH_2C_6H_5$). The base was isolated as an amorphous yellow substance, m.p. 142–146°; the hydrochloride melted at 204–207°.

O-Benzylpsychotrine was reduced in the presence of platinic oxide to O-benzylcephaeline (XXXIX, R = $CH_2C_6H_5$), the base melting at 137–140°.

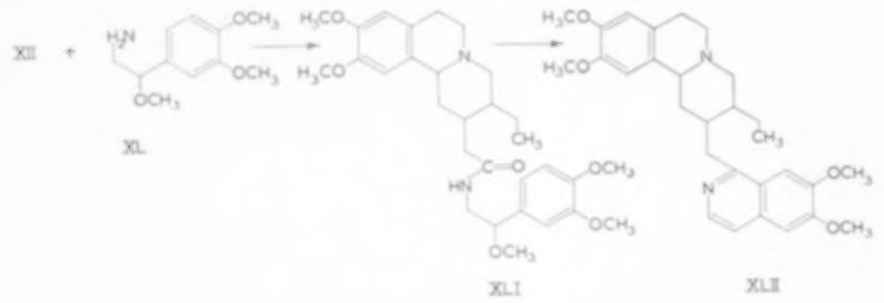
[23] K. E. Hamlin and F. E. Fischer, *J. Amer. Chem. Soc.* **75**, 5119 (1953).

The ultra-violet absorption spectra of the intermediates were similar to those of the intermediates in the synthesis of emetine.

Synthesis of emetamine

Emetamine differs from emetine in having four hydrogen atoms less. It was suggested in 1827 that the emetamine structure involves an *iso*quinoline ring whilst emetine is a derivative of tetrahydro*iso*quinoline. When the structure of emetine had been established, emetamine was assigned formula (XLII). Recently this structure has been confirmed by the investigation of the oxidation products of the bisbenzyl chlorides of emetamine and of O-methylpsychotrine.[24]

Following the scheme worked out for emetine, we carried out the synthesis[25] by condensation of the methyl ether (XII; R = CH_3) with β-(3:4-dimethoxyphenyl)-β-methoxyethylamine[26] (XL), as follows:



Heating ester (XII; R = CH_3) with (XL) gave the amide (XLI), isolated from ethanol as colourless crystals, m.p. 172·5–173·5°. Cyclisation of the amide with phosphorus oxychloride gave emetamine, m.p. 124–125°, and the oxalate, m.p. 141·5–142·5°. Oxidation of the (±)-base of emetamine with bromine resulted in rubremetamine bromide, obtained as orange-red crystals, m.p. 170–185°. The ultra-violet absorption spectrum of the synthetic rubremetamine bromide was found to be identical with that of the rubremetamine bromide produced from the natural alkaloid.

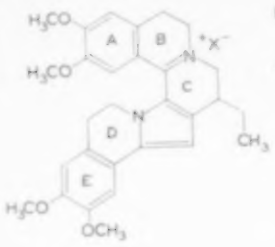
Synthesis of emetine analogues

One of the most interesting features in the chemistry of alkaloids of ipecacuanha is the oxidation of (−)-emetine with mild oxidising agents such as ferric chloride, bromine, iodine and mercuric acetate. The red compound isolated and referred to as dehydroemetine or rubremetine, $C_{23}H_{33}O_4N_2$, contains seven hydrogen atoms fewer than emetine. The formation of rubremetine is accompanied by structural changes, one of the nitrogen atoms losing its basicity and the second one becoming quaternary. Until recently the structure of rubremetine remained ambiguous until Openshaw succeeded in proving that its structure corresponded to (XLIII).[27]

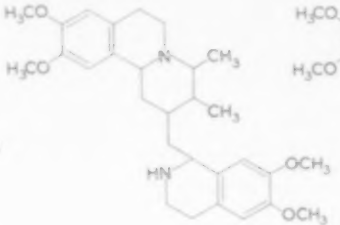
Formula (XLIII) accounts for all the chemical properties of this compound, including the fact that the oxidation of N-methylemetine cannot result in a substance

[24] A. R. Battersby, *Chemical Society Special Publication* No. 3, p. 36. London (1955).
[25] R. P. Evstigneeva, J. Braier and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR* **117**, 227 (1957).
[26] M. G. Tsatsas, *Bull. Soc. Chim. Fr.* **16**, 884 (1949).
[27] H. T. Openshaw, *Chemical Society Special Publication* No. 3, p. 28. London (1955).

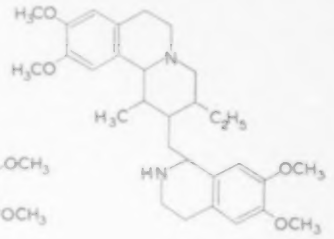
similar to rubremetine. In order to show the effect of substituents in the ring C on the formation of the red compound, the synthesis of two emetine analogues with alkyl substituents in two free positions at C_5 and C_6 was undertaken, namely 4′:5′-dimethoxy-:65-dimethyl-7-(1″-methyl-6″:7″-dimethoxy-1″:2″:3″:4″-tetrahydro-*iso*quinolyl)-3:4:5:6:7:8-hexahydrobenzo-1:2:1′:2′-quinolizine[28] (IV), and 8-methyl-emetine[29] (XLIV).



XLIII

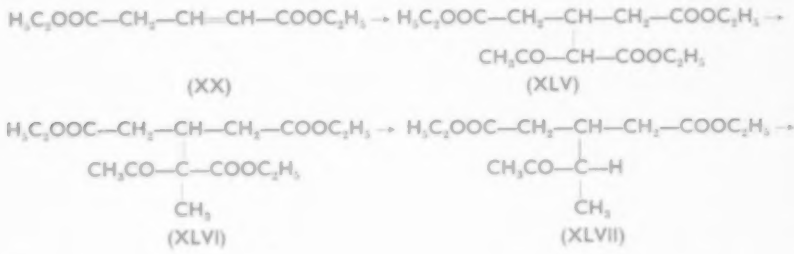


IV

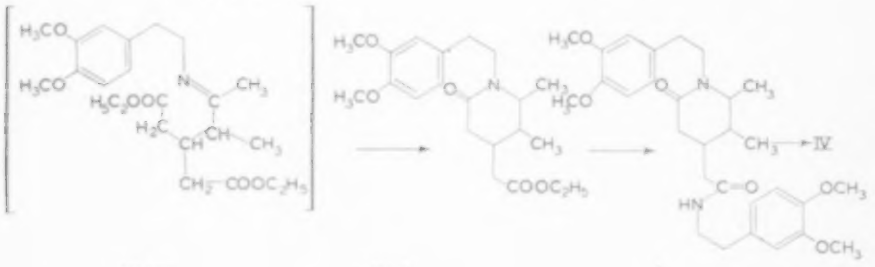


XLIV

The synthesis of (IV) was effected by starting with ethyl glutaconate, according to the scheme:



(XX) (XLV) (XLVI) (XLVII)



XLVIII XLIX L

By condensing ethyl glutaconate and acetoacetate ethyl β-(acetocarbethoxy) methylglutarate (XLV), b.p. 167–169°/2·5–3 mm, was obtained. On treatment with methyl halide it was converted into ethyl β-(α'-aceto-α' carbethoxy)ethylglutarate (XLVI), b.p. 149–151°/1·4 mm. The latter was saponified with sodium ethoxide and water to yield after decarboxylation ethyl β-(α'-aceto)ethylglutarate (XLVII), b.p. 110–112°/1 mm. This ester reacted readily with 1 mole of homoveratrylamine to

[28] R. P. Evstigneeva, N. M. Kashnikova, M. S. Bainova and N. A. Preobrazhensky, *Zh. Obschh. Khim.* **XXVIII**, 1184 (1958).
[29] R. P. Evstigneeva, L. V. Lavrova, C. D. Zarankina and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXVIII**, 1190 (1958).

form the Schiff's base (XLVIII), which was hydrogenated in the presence of platinic oxide. The reduction product was cyclised to the corresponding piperidone derivative (XLIX) by heating on a water-bath *in vacuo*. The resulting substance was condensed with a second molecule of homoveratrylamine by heating at 180°. The diamide (L), after cyclisation with phosphorus oxychloride and reduction of the quaternary chloride, yielded 4′:5′:-dimethoxy-5:6-dimethyl-7-(1″-methyl-6″:7″-dimethoxy-1″:2″:3″:4″-tetrahydro*iso*quinolyl)-3:4:5:6:7:8-hexahydrobenzo-1:2:1′:2′-quinolizine (IV) as a thick yellow oil, the melting point of the hydrochloride being 134–135°.

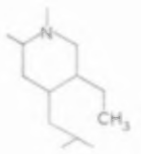
The synthesis of 8-methylemetine XLIV has been effected starting with ethyl acetonedicarboxylate, which was methylated by methyl halides to give ethyl α-methyl-acetonedicarboxylate, b.p. 118–119°/2 mm. The subsequent procedure was similar to that for emetine, requiring the preparation of the following: ethyl α-methyl-glutaconate, b.p. 104–105°/2 mm; ethyl α-methyl-β-cyano-β-carbethoxymethyl-glutarate, b.p. 155–156°/1 mm; ethyl α-methyl-β-(α′-cyano-α′-carbethoxy)propyl-glutarate, b.p. 158–159°/1 mm; ethyl α-methyl-β-(α′-cyano)propylglutarate, b.p. 130–132°/1 mm. The anhydrous ethyl chloride of the quinolizine derivative was isolated as an amorphous substance, m.p. 126–127°, the crystalline hydrate melting at 184–185·5°, and 8-methylemetine was produced as a yellow oil, the hydrochloride melting at 121–122°.

The bases of the emetine dimethyl analogue (IV) and 8-methylemetine (XLIV) were oxidised with bromine, the former giving an orange-red substance, m.p. 164–180°, whose ultra-violet spectrum was identical with that of rubremetine, the latter yielding a yellow substance, m.p. 195–198°, but, when oxidised with iodine, an amorphous yellow substance, m.p. 135–140°, is obtained, both substances being markedly different in their properties from rubremetine.

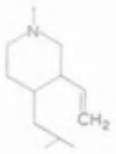
It follows that the alkyl substituent at C_8 hinders the formation of the red compound, thus confirming the participation of hydrogen atoms at C_8 in rubremetine formation from emetine.

Close relationship of isoquinoline, quinoline *and indole synthesis*

The results obtained from the synthetic investigation of the alkaloids of ipecacuanha enable us to turn to the syntheses of other substances involving a piperidine group similar to that (B) in emetine (A) such as meroquinene, homomeroquinene (B) and their dihydro derivatives.



A

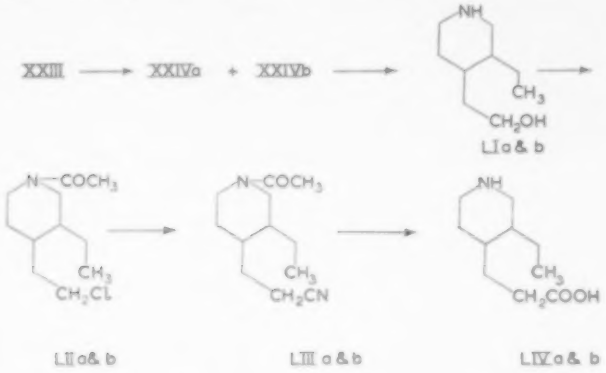


B

It has been shown that the use of the same starting compounds leads through a similar conversion to the synthesis of alkaloids of ipecacuanha and the cinchona bark alkaloids.[30]

[30] N. A. Preobrazhensky, R. P. Evstigneeva, G. S. Levtchenko and Fed'ushkina, *Dokl. Akad. Nauk SSSR* **81**, 421 (1951).

The scheme worked out required homocincholoipon and homomeroquinene. The synthesis of *cis*-homocincholoipon to obtain dihydroquinine was carried out with ethyl δ-ethyl-α-piperidone-γ-acetate (XXIV). The synthesis of the isomeric *cis*- and *trans*-homocincholoipons was also effected by starting with diethyl β-(α′-cyano) propylglutarate, the principal intermediate in the synthesis of ipecacuanha alkaloids, according to the following scheme.[31]



Hydrogenation of ethyl β-(α′-cyano)propylglutarate (XXIII; $R = C_2H_5$) gave 4-carboethoxymethyl-5-ethylpiperidone-2, isolated in two isomeric forms: (1) a crystalline substance (XXIVa), m.p. 84–85°, very sparingly soluble in ether and (2) an oily substance (XXIVb), b.p. 175–176°/1·5 mm, readily soluble in ether. Subsequently, both isomers were synthesised separately. The reduction of 4-carbo-ethoxymethyl-5-ethylpiperidones with lithium aluminium hydride gave 3-ethyl-4-(β-hydroxyethyl) piperidines (LIa and LIb), b.p. 131–132°/3 mm and 127–128°/2·5 mm, respectively. The treatment of the 3-ethyl-4-(β-hydroxyethyl)piperidine hydrochlorides with thionyl chloride gave 3-ethyl-4-(β-chloroethyl)piperidine hydrochlorides, which, without being isolated, were converted into N-acetyl-3-ethyl-4-(β-chloroethyl) piperidines (LIIIa and LIIIb), b.p. 156–157°/2 mm and 157–158°/2 mm, respectively. Treatment of these substances with potassium cyanide gave N-acetyl-3-ethyl-4-(β-cyanoethyl)piperidine, b.p. 165–168°/3 mm (LIIIa) and 168–172°/3 mm (LIIIb), which, on saponification gave 3-ethyl-4-(β-carboxyethyl)piperidines, or homocincholoipons (LIVa and LIVb).

The crystalline and oily isomeric forms of 4-carboethoxymethyl-5-ethylpiperidone-2 gave aurichlorides (homocincholoiponic aurichlorides) melting, respectively, at 174·4–175° and 194·5–195° and mixed melting point 155–151°.

The structural determination of the homocincholoipons was carried out by comparing the intermediates of homocincholoipon synthesis (LIa) and LIb with 3-ethyl-4 (β-hydroxyethyl)piperidine (LIc) produced from natural quinine via meroquinene, the piperidine products of quinine decomposition being known to retain the *cis*-configuration. The meroquinene ethyl ester was reduced with lithium aluminium hydride to 3-vinyl-4-(β-hydroxyethyl)piperidine.

The latter was hydrogenated in the presence of platinic oxide to give 3-ethyl-4-β-hydroxyethyl)piperidine (LIc), b.p. 115–116°/1·5 mm. The infra-red spectra of

[31] J. F. Malina, R. P. Evstigneeva and N. A. Preobrazhensky, *Chem. and Chem. Technol.* In press (1957).

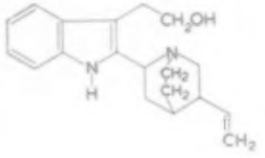
(LIa), (LIb) and (LIc) have substantiated the identity of our synthetic compounds with those obtained from the natural quinine. The spectrum of (LIb) produced from the oily 4-carboethoxymethyl-5-ethylpiperidone (XXIVb) differs from those of (LIa) and (LIc) in the 1290 cm^{-1} and 700–750 cm^{-1} range.

This data suggests that both the crystalline 4-carboethoxymethyl-5-ethylpiperidone-2 and the homocincholoipon synthetically obtained from it (LIVa) are *cis*, while the oily 4-carboethoxymethyl-3-ethylpiperidone-2 (XXIVb) and the homocincholoipon (LIVb) are *trans*.

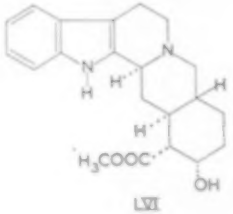
The synthetic routes of ipecacuanha alkaloids and those of the cinchona bark are thus very similar, the close relationship between these two alkaloids being also indicated by the theory of biogenesis.[32]

The alkaloids of cinchona bark are divided into two large groups, first, the quinoline derivatives such as quinine, quinidine, and cinchonine, and, secondly, the indole derivatives such as cinchonamine and quinamine. The syntheses of the major alkaloids of the quinoline series including that of quinine itself have already been effected, but the synthetic study of the quinine alkaloids of indole structure is far from being complete, although these substances are of great theoretical interest as being biogenetically and structurally related to such physiologically valuable organic compounds as yohimbine, reserpine (serpasil) and so on.

We have succeeded in finding synthetical routes for the quinine alkaloid of the indole group, cinchonamine (LV)[33] as a bridge between the quinine alkaloids of the quinoline series and the alkaloids of the indole series and have also effected the synthesis of yohimbine (LVI)[34]:



LV



LVI

These investigations are, however, beyond the scope of the present paper and will be reported later.

[32] R. Woodward, *Angew. Chem.* **68**, 13 (1956).
[33] Tcheng Tchang-by, R. P. Evstigneeva and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR*. In press (1958).
[34] L. A. Axanova and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR* **117**, 81 (1957).

Tetrahedron, 1958, Vol. 4, pp. 241–245. Pergamon Press Ltd., London

SUR LE COMPORTEMENT PHOTOCHIMIQUE DES 19-NOR $\Delta^{5,7}$-STEROIDES

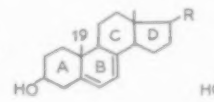
L. VELLUZ, B. GOFFINET et G. AMIARD
Services de Recherches Roussel-Uclaf, Paris

(*Received* 29 *April* 1958)

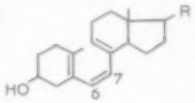
Résumé—Le 19-nor $\Delta^{5,7}$-androstadiène 3β, 17β-diol, préparé à partir de la 19-nor testostérone, donne naissance par irradiation ultra-violette à un photoisomère isolable sous forme de bis-dinitrobenzoate. D'après le spectre d'absorption U.V., on peut attribuer au composé obtenu la structure d'un 19-nor 17-hydroxy étiotachystérol.

Le 7-déhydro 19-nor cholestérol donne lieu par irradiation ultra-violette aux mêmes modifications spectrales.

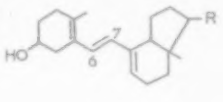
Il résulte de nos recherches antérieures[1,2] que l'irradiation ultra-violette de l'ergostérol (Ia) provoque l'ouverture du cycle B de ce stéroïde avec formation de *précalciférol* (IIa) et de *tachystérol* (IIIa). Le précalciférol et le tachystérol sont en relation d'isomérie *cis-trans* éthylénique par rapport à la double liaison 6–7.[2] D'autre part, le précalciférol se transforme facilement en *calciférol* (IVa) par une isomérisation non



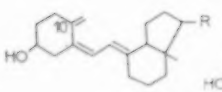
I



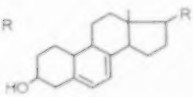
II



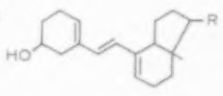
III



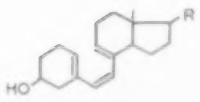
IV



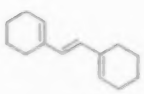
V



VI



VII



VIII

a) R = C_9H_{17}
b) R = C_8H_{17}
c) R = H
d) R = OH

[1] L. Velluz, G. Amiard et A. Petit, *Bull. Soc. Chim. Fr.* **16**, 501 (1949).
[2] L. Velluz, G. Amiard et B. Goffinet, *Bull. Soc. Chim. Fr.* 1341 (1955).

photochimique qui donne lieu à un équilibre.[1] Nous avons montré que ces diverses transformations apparaissent aussi lorsque la chaîne latérale est différente—série du

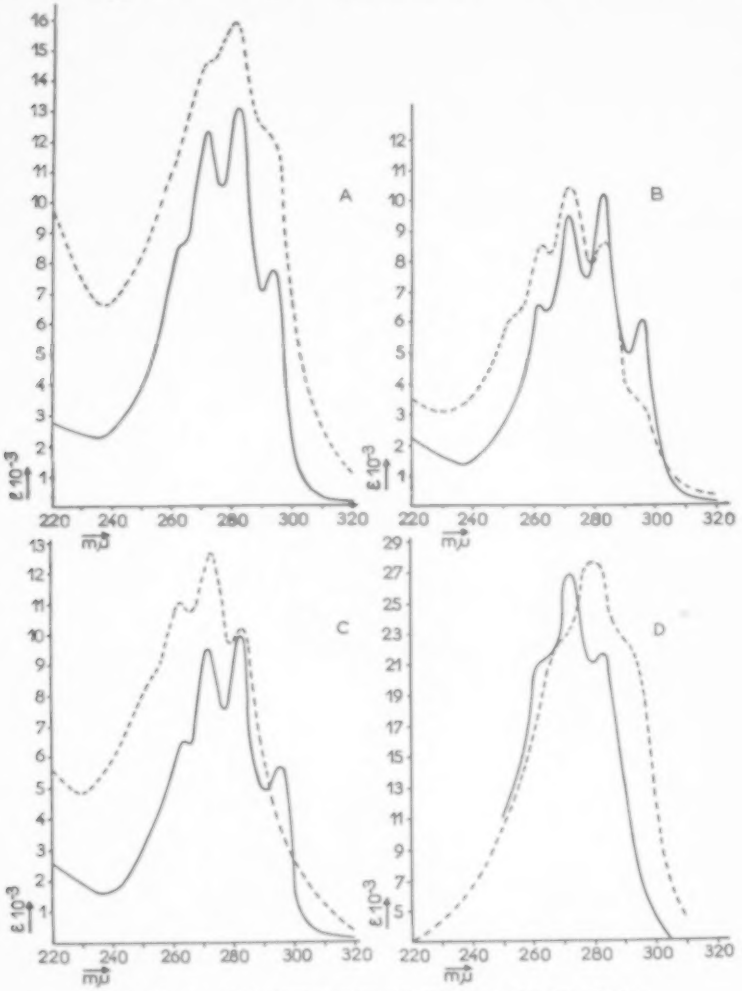


FIG. 1. Spectres d'absorption ultra-violette déterminés dans l'éther.
A—en trait plein: 7-déhydro cholestérol
en tirets: 7-déhydro cholestérol après 3 heures d'irradiation U.V.
B—en trait plein: 19-nor $\Delta^{5,7}$-androstadiène 3,17-diol
en tirets: 19-nor $\Delta^{5,7}$-androstadiène 3,17-diol après 30 minutes d'irradiation U.V.
C—en trait plein: 7-déhydro 19-nor cholestérol
en tirets: 7-déhydro 19-nor cholestérol après 1 heure d'irradiation U.V.
D—en trait plein: 19-nor 17-hydroxy étiotachystérol déterminé par soustraction graphique de l'absorption du dinitrobenzoate d'éthyle de celle de son dinitrobenzoate en solution alcoolique.
en tirets: tachystérol$_2$ d'après Havinga *et al.*, *Rec. Trav. Chim. Pays-Bas* **74**, 1230 (1955).

7-déhydro cholestérol (Ib à IVb)—et lorsqu'elle est absente ou remplacée par une fonction hydroxyle—séries étio (Ic à IVc) et hydroxy étio (Id à IVd).[3]

[3] L. Velluz, G. Amiard et B. Goffinet, *Bull. Soc. Chim. Fr.* 882 (1957).

Au cours des diverses isomérisations photochimiques et non photochimiques qui conduisent de l'ergostérol au calciférol et aussi dans le cas des analogues, le groupe méthyle angulaire 19 se transforme en groupe méthylénique. Il semblait donc intéressant d'étudier le comportement photochimique de $\Delta^{5,7}$-stéroïdes dépourvus de ce méthyle angulaire 19.

Nous avons irradié le 7-déhydro 19-nor cholestérol (Vb) que nous avons décrit précédemment[4] et le 19-nor $\Delta^{5,7}$-androstadiène 3β,17β-diol (Vd) que nous avons préparé à partir de la 19-nor testostérone.

Lorsqu'on irradie à froid, à la lumière ultra-violette, le 7-déhydro cholestérol (Ib) en éther, on constate une augmentation de l'absorption vers 280 mμ (Fig. 1A), ce qui traduit la formation de tachystérol$_3$(IIIb). Mais, par irradiation du 19-nor $\Delta^{5,7}$-androstadiène 3β, 17β-diol (Vd), on observe une augmentation plus lente de l'absorption qui présente à la fin un maximum principal vers 272 mμ (Fig. 1B). En traitant de la façon habituelle le produit d'irradiation, on isole le bis-3,5-dinitro benzoate cristallisé d'un isomère dont le spectre en alcool présente un fort maximum vers 272 mμ avec des maxima secondaires vers 263 et 284 mμ. L'augmentation de l'absorption U.V. constatée lors de l'irradiation est donc due à la formation de ce corps dont le spectre rappelle beaucoup celui du tachystérol$_2$ (Fig. 1D). D'après l'étude effectuée par Inhoffen[5,6] sur des modèles triéniques conjugués, un tel spectre correspondrait bien à la structure VId du 19-nor 17β-hydroxy étiotachystérol. En effet, pour le modèle VIII on observe des maxima à 260, 269 et 281 mμ. Comme l'adjonction du cycle D pentagonal provoque un déplacement bathochrome d'environ 6 mμ,[5] on obtiendrait pour VId des maxima à 266, 275 et 287 mμ. Les valeurs observées 263, 272 et 284 mμ sont donc en bon accord.

Dans le cas du 7-déhydro 19-nor cholestérol (Vb), l'étude spectrographique de l'irradiation conduit à des résultats analogues (Fig. 1C) qui traduisent la formation de 19-nor tachystérol$_3$ (VIb).

On peut donc conclure que la présence du groupe méthyle 19 n'est pas indispensable pour l'ouverture photochimique du cycle B des $\Delta^{5,7}$-stéroïdes, bien qu'elle semble la favoriser. En effet, la transformation s'opère mais elle est plus lente lorsque le méthyle angulaire est absent. Par contre, nous n'avons pas pu déceler, dans les produits d'irradiation, la présence d'autres corps que les 19-nor tachystérols (VI) en particulier des 19-nor précalciférols (VII).

PARTIE EXPERIMENTALE

3,17β-*Diacétoxy* 19-*nor* $\Delta^{3,5}$-*androstadiene*

On porte au reflux pendant trois heures, sous azote, 5 g de 19-nor testostérone dans 80 ml d'anhydride acétique, 32 ml de chlorure d'acétyle et 3,2 ml de pyridine. On chasse le solvant sous vide et cristallise en alcool. On obtient 5,5 g (85 %) de paillettes incolores brillantes, $F = 176$–$177°$, $[\alpha]_D^{20} = -155° \pm 2$ ($c = 2\%$, chloroforme), $\lambda_{max} = 235$ mμ ($\varepsilon = 18.950$, alcool). Hartmann *et al.*[7] indiquent: $F = 170$–$174°$, $[\alpha]_D^{24} = -151{,}2°$ (chloroforme), $\lambda_{max} = 234$ mμ ($\varepsilon = 21.000$).

[4] L. Velluz, B. Goffinet, J. Warnant et G. Amiard, *Bull. Soc. Chim. Fr.* 1289 (1957).
[5] H. H. Inhoffen, K. Brückner, R. Gründel et G. Quinkert, *Chem. Ber.* **87**, 1407 (1954).
[6] H. H. Inhoffen et G. Quinkert, *Chem. Ber.* **87**, 1418 (1954).
[7] J. A. Hartmann, A. J. Tomasewski et A. S. Dreiding, *J. Amer. Chem. Soc.* **78**, 5662 (1956).

17β-Acétoxy 19-nor $\Delta^{4,6}$-androstadiène 3-one

(a) *Bromuration.* A une suspension de 5 g de 3, 17β-diacétoxy 19-nor $\Delta^{3,5}$-androstadiène dans 25 ml d'acide acétique et 15 ml de collidine, on ajoute, à 10°, sous azote, 24 ml de solution acétique de brome à 10% puis verse dans une solution de 125 g de bicarbonate de sodium dans 200 ml d'eau en présence de 100 ml d'éther. La solution éthérée est lavée à l'eau et séchée.

(b) *Débromhydratation.* Au mélange de 5 g de bromure de lithium et 5 g de carbonate de lithium dans 80 ml de diméthylformamide chauffé à 100° sous agitation, on ajoute la solution éthérée obtenue précédemment puis, après distillation de l'éther, on maintient dix-sept heures à 100° en atmosphère d'azote et sous agitation. Après refroidissement, on verse dans 200 ml d'eau glacée et 16 ml d'acide acétique. Par extraction à l'éther, on recueille 4,4 g de produit brut qu'on purifie par recristallisation en éther de pétrole puis en méthanol aqueux à 60%. On obtient des prismes, $F = 68°$ (déc.), $[\alpha]_D^{20} = -36° \pm 2$ ($c = 1\%$, chloroforme), $\lambda_{max} = 284$ mμ ($\varepsilon = 27.500$, alcool).

Anal. :	$C_{20}H_{26}O_3 = 314,4$,	Calc. %:	C 76,4	H, 8,3	O 15,3
		Tr. :	76,4	8,3	14,9

3,17β-Diacétoxy 19-nor $\Delta^{3,5,7}$-androstatriène

On traite 4,1 g du produit brut précédent selon le mode opératoire utilisé pour le 3,17β-diacétoxy 19-nor $\Delta^{3,5}$-androstadiène par 50 ml d'anhydride acétique, 20 ml de chlorure d'acétyle et 2 ml de pyridine. On recristallise en alcool à l'abri de l'air et en présence d'un antioxygène. On obtient des aiguilles jaunissant très rapidement à l'air et à la lumière. Rendement: 55% à partir du diacétate de nor-testostérone. $F = 158$–$159°$ (déc.), $[\alpha]_D^{20} = -30° \pm 2$ ($c = 1\%$, chloroforme), $\lambda_{max} = 290$, 300, 313 et 327,5 mμ ($\varepsilon = 11.580$, 18.000, 22.350 et 16.200, alcool).

Anal. :	$C_{22}H_{28}O_4 = 356,4$,	Calc.% :	C 74,1	H 7,9	O, 18,0
		Tr. :	74,1	7,8	17,8

19-Nor $\Delta^{5,7}$-androstadiène 3β,17β-diol, Vd.

On réduit, par deux heures de chauffage au reflux sous azote, 3,15 g du diacétate précédent dans 20 ml de tétrahydrofuran, 20 ml de méthanol et 20 ml d'eau par 4 g d'hydroborure de potassium. On refroidit, acidifie à pH5 par l'acide acétique et précipite par 300 ml d'eau glacée. Le produit brut est saponifié par reflux de trente minutes dans 40 ml de méthanol et 20 ml de potasse méthanolique à 20%. On sépare le produit par concentration de la solution méthanolique et dilution par 100 ml d'eau. Après recristallisation en alcool, on obtient 1,65 g (67%) de paillettes incolores, $F = 195$–$197°$, $[\alpha]_D^{20} = +226° \pm 4$ ($c = 1\%$, pyridine), λ_{max}: 272, 283 et 295 mμ ($\varepsilon = 11.170$, 11.650 et 6.580, alcool).

Anal. :	$C_{19}H_{28}O_2$, $1/4H_2O = 278,9$	Calc. %:	C 77,5	H 9,6	O 12,9
		Tr. :	77,2	9,7	12,8

Diacétate. On acétyle par l'anhydride acétique en pyridine à température ambiante

et recristallise en méthanol. On obtient des paillettes brillantes incolores, $F = 129$–$130°$, $[\alpha]_D^{20} = +212° \pm 2$ ($c = 1\%$, chloroforme).

Anal. :	$C_{22}H_{30}O_4 = 358{,}5$,	Calc. %:	C 73,7	H 8,4	O 17,85
		Tr. :	73,7	8,4	17,8

Bis-3,5-*dinitro benzoate*. On estérifie par le chlorure de 3,5-dinitro benzoyle en présence de pyridine en solution benzénique à 40° et recristallise en benzène-alcool. On obtient des prismes orangés, $F = 224$–$225°$, $[\alpha]_D^{20} = +155° \pm 2$($c = 1\%$, chloroforme).

Anal. :	$C_{32}H_{30}O_{12}N_4 = 662{,}6$,	Calc.%:	C 58,0	H 4,6	N 8,5	O 29,0
		Tr. :	58,0	4,4	8,3	28,9

Bis-3,5-*dinitro benzoate du* 19-*nor* 17β-*hydroxy étiotachystérol*

On irradie par une lampe U.V. Hanau pendant 45 minutes à 0°, sous agitation et sous atmosphère d'azote, 0,25 g de 19-nor $\Delta^{5,7}$-androstadiène 3β,17β-diol dans 1.200 ml d'éther en présence de 10 mg d'hydroquinone. On chasse l'éther à 0° et estérifie le résidu par 5 g de chlorure de 3,5-dinitro benzoyle dans 40 ml de benzène et 10 ml de pyridine en deux heures à température ambiante.

On isole le bis-dinitrobenzoate brut de la manière usuelle, répète 5 fois l'opération et réunit les produits qu'on chromatographie sur alumine lavée à l'acide. L'éluat benzénique concentré à 30 ml laisse déposer 1,6 g de bis-dinitrobenzoate du produit initial. $F = 210$–$215°$ (44%).

Une chromatographie effectuée sur le résidu de la solution mère permet d'obtenir 0,226 g de bis-3,5-dinitrobenzoate de 19-nor hydroxyétiotachystérol qu'on recristallise en benzène-alcool-éther. $F = 130$–$132°$, $[\alpha]_D^{20} = +87° \pm 4$($c = 1\%$, chloroforme). Spectre U.V. (alcool) après déduction de l'absorption des groupes dinitro benzoyle: λ_{max}: 263, 272,5 et 283,5 mμ (ε = 21.300, 27.000 et 21.800).

Anal. :	$C_{32}H_{30}O_{12}N_4 = 662{,}6$,	Calc.%:	C 58,0	H 4,6	N 8,5	O 29,0
		Tr. :	58,1	4,5	8,3	28,8

Tetrahedron, 1958, Vol. 4, pp. 246–255. Pergamon Press Ltd., London

THE CHEMISTRY OF CADINENES AND CADINOLS

V. HEROUT and V. SÝKORA
Department of Natural Products, Institute of Chemistry, Czechoslovak Academy of Science, Prague 6. Dejvice, Na Cvicisti 2

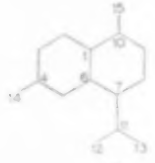
(*Received* 6 *May* 1958)

Abstract—A number of sesquiterpenoid hydrocarbons, the cadinenes, and tertiary alcohols, the cadinols, have been isolated in a pure state in these Laboratories during the past few years. Their constitution and absolute configuration have been established. This review is intended to be a brief survey of the history of these compounds as well as a summary of our results.

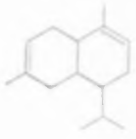
VOL. 4 1958

THE sesquiterpenoid hydrocarbons $C_{15}H_{24}$ (cadinenes) and tertiary alcohols $C_{15}H_{26}O$ (cadinols) have long been known.[1,2,3,4] Soubeiran and Capitaine[5] prepared crystalline cadinene hydrochloride from cubeba oil. On account of the ready formation of this derivative, cadinene was detected in a number of ethereal oils.[2] Wallach[6] was the first to use the name cadinen for these hydrocarbons. A number of investigators, particularly Semmler and his co-workers, examined the chemistry of the cadinenes, but, the most important contribution to the elucidation of their structure was made by Ruzicka and his collaborators,[7] who dehydrogenated cadinene to cadalene (I) and proved its structure. The location of the double bonds in the cadinene skeleton (II) was achieved by the elegant work of Campbell and Soffer[8] who showed that the so-called β-cadinene which could be re-generated from cadinene hydrochloride has structure (III).

I



II



III

Semmler and Jonas[9] isolated the first cadinol from galbanum oil, and later, a number of other cadinols yielding cadinene dihydrochloride were isolated (cf. ref. 1–4). This indicates that the cadinols possess the same carbon skeleton as cadinene, and that the double bond and the hydroxyl group must be attached to the same carbon atoms.

Since most of the cadinols and all the cadinenes which have been described were obtained as liquids (by fractional distillation without the use of efficient columns), it is evident that they must have been mixtures. These could be characterised either

[1] J. Simonsen, D. H. R. Barton and L. N. Owen, *The Terpenes* Vol. III. Cambridge University Press (1952).
[2] *Elsevier's Encyclopedia of Organic Chemistry* (Edited by F. Radt) Ser. III, Vol. 12B, pp. 176–188, 322–324 and 1434–1437.
[3] A. J. Haagen-Smit, *Fortschr. Chem. Org. Naturstoffe* **12**, 1 (1955).
[4] D. H. R. Barton, *Quart. Rev.* **11**, 189 (1957).
[5] E. Soubeiran and H. Capitaine, *Liebigs Ann.* **34**, 323 (1840).
[6] O. Wallach, *Liebigs Ann.* **271**, 297 (1892).
[7] L. Ruzicka, *Über Konstitution und Zusammenhänge in der Sesquiterpenreihe*. Bornträger, Berlin (1928).
[8] W. P. Campbell and M. D. Soffer, *J. Amer. Chem. Soc.* **64**, 417 (1942).
[9] F. W. Semmler and K. G. Jonas, *Ber. Dtsch. Chem. Ges.* **47**, 2073 (1914).

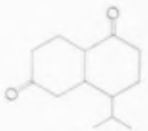
by the formation of cadinene dihydrochloride (or dihydrobromide) or by dehydrogenation to cadalene which forms a number of crystalline derivatives. In order to distinguish the different cadinenes and cadinols the prefixes *d*- and *l*- indicating only the direction of the optical rotation, were used at first. These compounds were not true antipodes as was sometimes claimed in the literature[1] since both dextro- and laevo-rotatory cadinenes and cadinols afforded only (—)-cadinene-dihydrochloride or -dihydrobromide. Ruzicka and Stoll[10] introduced a better system of notation based on Greek letters as prefixes for compounds of the cadinane series which differed in the position of the double bonds. Recently we proposed a rational nomenclature derived from the root cadin-[11] for cadinane derivatives having skeleton (II). The numbering of the skeleton is based on the principle formulated by Barton and his collaborators.[12] Its advantages lie in the fact that it relates the cadinane carbon atoms with those of other sesquiterpenoid derivatives, e.g. those of selinane (= eudesmane) and guaiane. This nomenclature is not limited to substances which yield cadinene dihydrochloride, but is applicable to all compounds possessing the cadinane skeleton.

In recent years better techniques for the isolation and identification of cadinenes and cadinols have become available, permitting the isolation of a number of cadinenes and cadinols in a relatively pure state. Table 1 summarises the physical constants of the cadinenes thus obtained.

Substance (IV) (α-cadinene) is not known, although Briasco and Murray assigned this structure to a hydrocarbon from Dacrydium Colensoi[13] but no proof of this formulation was provided.* A β-cadinene ($[\alpha]_D^{20°}$ −130°[2]) obtained by the dehydrohalogenation of (—)-cadinene dihydrochloride has been described in the literature; it is, in fact, a mixture of cadinenes. Campbell and Soffer[8] showed that the principal component of the mixture was the hydrocarbon (III). We have recently obtained a sample of very pure β-cadinene with a high optical rotation ($[\alpha]_D^{20°}$ −251°) by fractionation through an efficient column.[37] In the course of this distillation was also separated a small amount of a hydrocarbon with a methylene group. Its physical constants $d_4^{20°}$ 0·9298, $n_D^{20°}$ 1·5099, $[\alpha]_D^{20°}$ −13·3°) suggest that it may be identical with the so-called γ_1-cadinene described by Bhattacharyya and his co-workers[15,16] (see below).

IV

VI resp. VII



IX

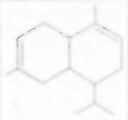
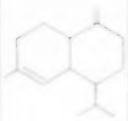
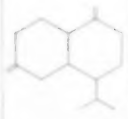
Kafuku and his collaborators[17] isolated a hydrocarbon from oil of citronella which they termed γ-cadinene. This hydrocarbon was separated[14] in a comparatively

* The authors reversed the terms α- and β-cadinene contrary to Ruzicka's original proposal;[10] cf. also Herout *et al.*[14]

[10] L. Ruzicka and M. Stoll, *Helv. Chim. Acta* **7**, 84 (1924).

[11] O. Motl, V. Sýkora, V. Herout and F. Šorm, *Chem. Listy* **52**, 316 (1958).
[12] D. H. R. Barton, P. de Mayo and M. Shafiq, *J. Chem. Soc.* 929 (1957).
[13] J. D. Briasco and J. Murray, *J. Appl. Chem.* **2**, 187 (1952).
[14] V. Herout, T. Kološ and J. Pliva, *Chem. Listy* **47**, 440 (1953); *Coll. Trav. Chim. Tchécosl.* **18**, 886 (1953).
[15] K. K. Chakravarti and S. C. Bhattacharyya, *Perf. & Ess. Oil Rec.* 365 (1955).
[16] B. B. Ghatgey, R. K. Razdan and S. C. Bhattacharyya, *Perf. & Ess. Oil Rec.* 157 (1956).
[17] K. Kafuku, T. Ikeda and Y. Fujita, *J. Chem. Soc. Japan* **53**, 636 (1932); *Chem. Abstr.* **27**, 280 (1933).

TABLE I. SURVEY OF KNOWN CADINENES[a]

Name[b]	No.	Formula	d_4^{20}	n_D^{20}	$[\alpha]_D$	Infra-red frequency of double bond	Ref
β-cadinene Cadina-3,9-diene	III		0·9239	1·5059	−251	790,812, 822 cm^{-1}[c]	37
γ-Cadinene Cadina-4,10 (15)-diene	VII		0·9125	1·5075	+148°	794,836 cm^{-1}[c] 890 cm^{-1}[d]	14
γ$_1$-Cadinene Cadina-4(14), 9-diene	V		—	*1·5155*[e]	*−19°*[f]		16
δ-Cadinene Cadina-4,10 (1)-diene	VIII		0·9175	1·5086	+94°	836 cm^{-1}[c]	14
ε-Cadinene Cadina-4(14),10 (15)-diene	X		0·9107	1·5038	+47°	890 cm^{-1}[d]	20

[a] The data obtained in these Laboratories are printed in ordinary type, those of other authors are *italicised*.

[b] The trivial names are given first, followed by the systematic names based on the nomenclature introduced by us.[11,38]

[c] Frequencies of trisubstituted double bonds.

[d] Frequency of methylene double bond.

[e] At 26·5°.

[f] The original paper records this value as "optical rotation".

pure state ($[\alpha]_D^{20°}$ +148°) from the same oil by fractional distillation and chromatography on alumina. The infra-red spectrum of the γ-cadinene obtained had a distinct band due to a methylene group and bands due to a trisubstituted double bond (see Table 1). In agreement with this observation the compound yielded the theoretical amount of formaldehyde (corresponding to one methylene group[18] on quantitative ozonolysis); and cadinene dihydrochloride in high yield.

Chakravarti and Bhattacharyya[15] have recently isolated a laevorotatory cadinene from Malabar lemon grass oil. Ghatgey, Razdan and Bhattacharyya[16] established structure (V) for this compound and named it γ_1-cadinene. Dev and Guha[19] demonstrated the presence of the same hydrocarbon in the sesquiterpenoid fraction from the oil of Hardwickia pinnata. In view of the fact that our γ-cadinene is not identical with γ_1-cadinene as shown by the marked difference in their optical rotations, we were able to postulate that the methylene group in γ-cadinene is attached to $C_{(10)}$ in the cadinane skeleton and that it must therefore have structure (VI) or (VII). Conclusive evidence for structure (VII) was obtained by the pyrolysis of α-cadinol *p*-nitrobenzoate (see below) to γ-cadinene.[18]

Another dextrorotatory cadinene, which affords (—)-cadinene dihydrochloride in high yield, was isolated from a number of essential oils (oil of ylang-ylang,[20] citronella,[14] sweet-flag,[21] oil of false cubebs[22]). This was termed δ-cadinene,[23] and its infra-red spectrum displayed absorption bands due to double bonds (cf. Table 1) indicating the absence of a methylene group and showing that the two double bonds are located in positions different from those in β-cadinene. On the basis of these facts structure (VIII) was assigned[23] to δ-cadinene. Corroborating evidence for this structure was obtained from the observation that the two epoxide groups in δ-cadinene dioxide are considerably less reactive[24] than the epoxide groups in β-cadinene dioxide.[8]

The so-called ε-cadinene[20] was isolated from oil of ylang-ylang. This substance also affords (—)-cadinene dihydrochloride. Ozonisation gives rise to two molecules of formaldehyde and the crystalline diketone (IX),[24] indicating that both double bonds must be present as methylene groups (see also infra-red absorption bands, Table 1). ε-Cadinene must therefore have structure (X). Dev and Guha[19] also demonstrated the presence of ε-cadinene in the mixture of cadinenes obtained from Hardwickia pinnata.

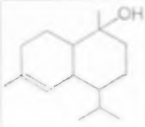
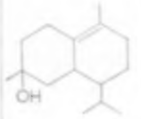
The isolation of β, γ, γ_1, δ and ε-cadinene proves the existence of five positional isomers of cadinene, although nine hydrocarbons, having double bonds attached to $C_{(4)}$ and $C_{(10)}$ and being able to yield (—)-cadinene dihydrochloride, are theoretically possible.

The cadinols isolated by earlier workers were generally obtained as liquids whose individuality was not rigorously established, (for a review see, e.g., refs. 1, 2). Only in recent times have some cadinols been obtained in a crystalline state (see Table 2).

[18] V. Sýkora and V. Herout, *Chem. Listy* In press.
[19] S. Dev and P. C. Guha, *J. Indian Chem. Soc.* **26**, 263 (1949).
[20] V. Herout and D. J. Dimitrov, *Chem. Listy* **46**, 432 (1952).
[21] F. Šorm, M. Holub, V. Sýkora, J. Mleziva, M. Steribl, J. Plíva, B. Schneider and V. Herout, *Chem. Listy* **46**, 554 (1952); *Coll. Trav. Chim. Tchécosl.* **18**, 512 (1953).
[22] F. Vonášek. Private communication.
[23] J. Plíva, V. Herout, B. Schneider and F. Šorm, *Chem. Listy* **46**, 410 (1952); *Coll. Trav. Chim. Tchécosl.* **18**, 500 (1953).
[24] V. Herout, F. Šantavý, *Chem. Listy* **47**, 70 (1953); *Coll. Trav. Chim. Tchécosl.* **19**, 118 (1954).

The first crystalline cadinol was obtained by Plattner and Márkus[25] from Javanese citronella oil. The same alcohol was isolated by Kritchevski and Anderson[26] from Chamecyparis lawsoniana Stump and Heartwood, and by workers in this Laboratory,[11]

TABLE 2. SURVEY OF KNOWN CRYSTALLINE CADINOLS[a]

Name[b]	No.	Formula	M.p.	$[\alpha]_D$	Infra-red frequency of double bond	Lit.
α-Cadinol Cadina-4-en-10-ol	XI		*72·5* 74·5 *74·8–75·4*	*−39·4* −47 *−38·5*	815 cm^{-1}[c]	25 11 26
δ-Cadinol[d] Cadina-1(10)-en-4-ol	XV		139–140 *138·5–139*	−109 *−107*		11 28
Cadinol of unknown constitution			78·5–79	−89	831 cm^{-1}[c]	11
Sesquigoyol[e]			*135·5*	*+99·5*	——	29

[a] The data obtained in these Laboratories are printed in ordinary type; those of other authors are *italicised*.

[b] The trivial names are given first followed by the systematic names based on the nomenclature introduced by us.[11,26]

[c] Frequency of trisubstituted double bond.

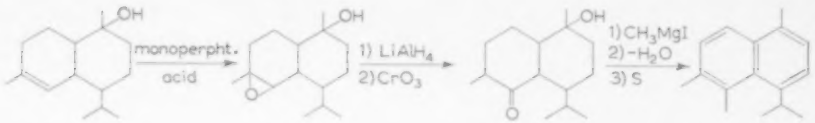
[d] A laevorotatory cadinol of m.p. 137·5–138·5°, which was isolated from Dictyopteris divaricata,[27] might be identical with δ-cadinol.

[e] Affords (+)-cadinene dihydrochloride.

from *Juniperus communis* L. We have recently been able to elucidate its structure by converting it into the keto-alcohol (XIII) via the epoxy-alcohol (XII). Methylation of the keto-alcohol (XIII) by means of Grignard reagent followed by dehydrogenation afforded 1:5:6-trimethyl-4-*iso*propylnaphthalene (XIV). This reaction sequence

[25] P. A. Plattner and R. Márkus, *Helv. Chim. Acta* **25**, 1674 (1942).
[26] G. Kritchevsky and A. B. Anderson, *J. Amer. Pharm. Assoc.* **44**, 535 (1955).
[27] M. Takaoka and Y. Ando, *J. Chem. Soc. Japan*, Pure Chem. Sect. **72**, 999 (1951); *Chem. Abstr.* **46**, 9261 (1952).

indicates structure (XI) for this alcohol and hence the name α-cadinol. (cf. ref. 1). Soffer and his collaborators[30] have reached the same conclusion independently.



XI XII XIII XIV

Erdtman *et al.* isolated a crystalline cadinol from the conifer *Pilgerodendron uviferum* (D. Don) Florin which they termed pilgerol.[28] The same alcohol was isolated in this Laboratory from oil of juniper berries and, more recently, from oil of false cubebs.[22] Contrary to the results of Erdtman *et al.* we found that the infra-red spectrum of this alcohol does not contain bands characteristic of a trisubstituted double bond nor of a methylene group. This pointed to the fact that the double bond is tetrasubstituted and that the alcohol must therefore have structure (XV) and be termed δ-cadinol. This was confirmed[11] by the ozonisation of δ-cadinol to a compound $C_{15}H_{26}O_3$, whose infra-red spectrum exhibited an intense band at 1708 cm^{-1} due to a keto group and a band at 3400 cm^{-1} due to a hydroxyl group. The above compound does not contain an aldehyde group in accordance with the postulated structure for δ-cadinol. The product of ozonolysis can thus be formulated as (XVI).

XV XVI

Another crystalline cadinol of m.p. 78·5–79° was also isolated from oil of juniper berries.[11] Its structure is being investigated at present.

Mention should also be made of the so-called taiwanol[31] (from Taiwania cryptomerioides Hayata) which is not crystalline but affords a solid phenylurethane of m.p. 134–135°. The alcohol torreyol[32] (from *Torreya nucifera* S. et Z.; m.p. 139–140°; $[\alpha]_D^{20°}$ +107·1°) cannot be definitely regarded as a cadinol. Although the authors record that it affords cadinene dihydrochloride, this fact conflicts with the observation that acetone is formed from it on ozonolysis. The physical constants of torreyol are strikingly close to those of the so-called sesquigoyol (from Pinus pentaphylla, m.p. 135·5°, $[\alpha]_D^{20}$ +99·5°) but the latter affords (+)-cadinene dihydrochloride.[29]

It may thus be said that only three cadinols have been firmly established out of the twelve theoretically possible forms which can give rise to (—)-cadinene dihydrochloride.

So far, only Ruzicka and his collaborators have studied the stereochemistry of cadinane derivatives. By comparing the physical constants of a number of substituted decalins the above authors concluded that the fusion of the two rings in the cadinane

[28] H. Erdtman, Z. Pelchowitz and J. G. Topliss, *Acta Chem. Scand.* **10**, 1563 (1956).
[29] Y. Sebe, *J. Chem. Soc. Japan* **61**, 1269 (1940); *Chem. Abstr.* **37**, 4064 (1943).
[30] M. D. Soffer, M. Brey and J. Fournier, *Chem. & Ind.* **19**, (1958).
[31] K. Kafuku and R. Kato, *Bull. Chem. Soc. Japan* **6**, 65 (1931); *Chem. Abstr.* **25**, 3125 (1931).
[32] K. Nishida, H. Uota, *J. Soc. Chem. Ind. Japan*, Suppl. bind. **43**, 64 (1940); *Chem. Abstr.* **34**, 6936 (1940); *J. Soc. Chem. Ind. Japan*, Suppl. bind. **44**, 119 (1941); *Chem. Abstr.* **38**, 4262 (1944).

skeleton i cis[1], but, their method did not lead to the correct results as shown by the similar case of eudesmol.[33]

Since cadinane derivatives afford the crystalline (—)-cadinene dihydrobromide (or dihydrochloride), physical rather than chemical methods seemed to be indicated for determining the relative configuration at all the asymmetric centres. Purely chemical methods do not appear to be practicable in the case of cadinane derivatives. Cadinene dihydrobromide is particularly suitable for X-ray diffraction measurements on account of the presence of the two heavy atoms in the molecule. The measurements were carried out at our suggestion by Hanic[34] who showed that it may be represented by formula (XVIIb) or its mirror image. Thus the two rings are trans-fused, the three alkyl groups are equatorial and the two halogen atoms are axial and lie on the same side of the molecule. The results of dipole moment measurements (cadinene dihydrochloride 4·06*D*, cadinene dihydrobromide 4·20*D*; Jehlička and Reiser[35]) are in accordance with this structure.

Hence all compounds affording (—)-cadinene dihydrobromide (or the corresponding dihydrochloride) must have the same configuration at $C_{(1)}$, $C_{(6)}$ and $C_{(7)}$ (see formula II) which are not involved in the formation of the derivative. It only remained to establish the absolute configuration of at least one of the asymmetric carbon atoms in order to elucidate the absolute configuration of all the centres of asymmetry.

For this reason the isolation of optically active *iso*propylsuccinic acid[36,37] from the products of oxidative degradation of β-cadinene was attempted.

Paper chromatography by the method of Šanda, Procházka and Le Moal[38] permitted the detection of a C_7 carboxylic acid in the mixtures obtained by the oxidation of β-cadinene with various reagents. The same method was also employed as a check during the isolation and final stages of purification of *iso*propylsuccinic acid. Nitric acid was used for the degradation starting with either β-cadinene or its ozonolysis product. The *iso*propylsuccinic acid thus obtained was found to be D-(+)-*iso*propylsuccinic acid (XVIII).[36,37]* Hence structure (XVIIa) and (XVIIb) could be assigned to cadinene dihydrochloride and dihydrobromide, respectively.

Evidence for the absolute configuration of cadinane derivatives was also obtained by a different method. Two crystalline ketones, which were isolated in the course of investigation[11] of the constitution of α-cadinol, were shown to have the absolute configuration represented by (XIX) and (XX). This was achieved by means of the method of rotatory dispersion curves which has recently been developed by Djerassi (cf. ref. 39, 40). Fig. 1 shows the dispersion curves of these ketones and of ketone (XXI) whose configuration has been established by Djerassi.[41]† The rotatory dispersion

* We are indebted to Prof. A. Fredga, of the University of Uppsala, for kindly supplying a specimen for reference.

† We are indebted to Prof. C. D. Djerassi, of Wayne University, Detroit, for measuring the rotatory dispersion curves of our ketones and for supplying reference compounds prior to publication.

[33] R. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 313 (1954).

[34] F. Hanic, *Chem. Listy* **52**, 165 (1958).

[35] V. Jehlička and A. Reiser, *Chem. Listy* in press.

[36] V. Herout and V. Sýkora, *Chem. & Ind.* 130 (1958)

[37] V. Sýkora, V. Herout and F. Šorm, *Chem. Listy* In press.

[38] V. Šanda, Z. Procházka and H. Le Moal, *Chem. Listy* In press.

[39] C. Djerassi, *Bull. Soc. Chim. Fr.* 741. (1957)

[40] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).

[41] C. Djerassi and D. Marschall, *J. Amer. Chem. Soc.* **80**, In press.

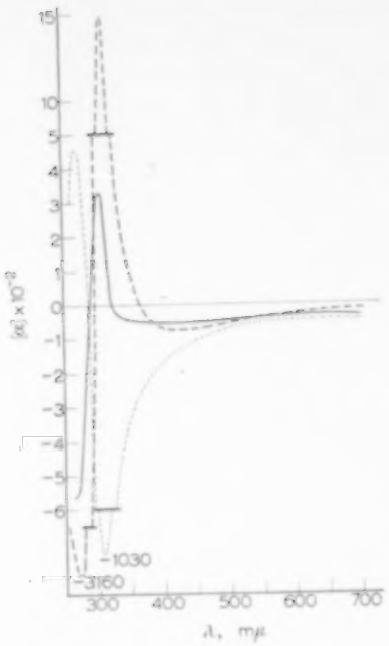
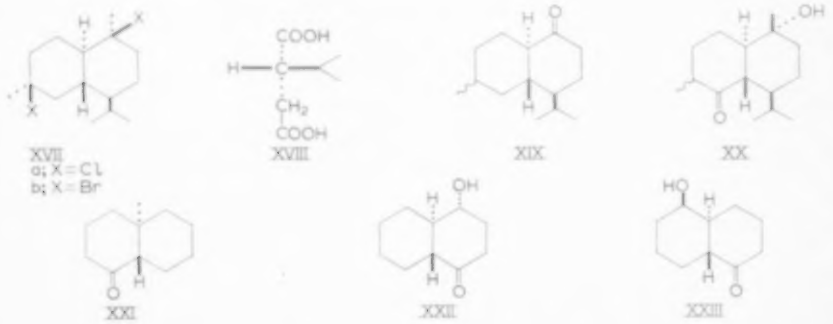


FIG. 1. Rotational dispersion curves.

10-desmethylcadinan-10-one (XIX; - - - -), cadinan-10-ol-5-one (XX; — — —), and *trans*-10-methyldecal-1-one (XXI; ———).

curves of the hydroxydecalones (XXII) and (XXIII), prepared by Prelog *et al.*[42*] are in good agreement with our results.



The above-mentioned findings permit the assignment of configuration to a number of other compounds. (see Table 3). The configuration of the hydroxyl groups of α-cadinol (XI) and δ-cadinol (XV) was deduced from the ease of esterification and, in the case of α-cadinol, also from the manner of dehydration.[11] The position of the

* We thank Prof. Prelog, E.T.H., Zurich, for kindly supplying this material prior to publication.

[42] V. Prelog *et al.*, *Helv. Chim. Acta* **41**, In press.

three-membered ring in the tricyclic hydrocarbon copaene[43] (XXIV or XXV), another compound which affords (—)-cadinene dihydrochloride, has not so far been established. The asymmetric centres at $C_{(1)}$ and $C_{(7)}$ must have the same absolute configuration as the corresponding carbon atoms in (—)-cadinene dihydrobromide.

Beside (—)-cadinene dihydrochloride, the (+)- and (±)-enantiomers[2,45] are also known. (+)-Cadinene dihydrochloride was prepared from sesquigoyol[29] (see above) and from a number of cadinenes isolated from various plants.[44–46] (cf. also ref. 2) The earliest data concerning the preparation of (+)-cadinene dihydrochloride[44] must be accepted with certain reservations in view of the low optical rotation of the material. It would be remarkable, from a biogenetic point of view, if it were proved that the same plant could produce different sesquiterpene enantiomers under different conditions.[45]

A number of compounds having skeleton (I), which do not afford cadinene dihydrochloride, are known. They are termed *iso*cadinenes[2] but their individuality is in doubt. *iso*-Zingiberene which was obtained from its dihydrochloride by regeneration, is the only compound which may be regarded as homogeneous; it has been assigned[47] structure (XXVI).* Sesquibenihene, which according to Katsura[49] has structure (XXVII), has also been investigated.

Hydrocarbons of molecular formula $C_{15}H_{22}$ and $C_{15}H_{20}$, which possess the cadinene skeleton, have been described. The former compound, calamene, was isolated from oil of sweet flag.[1,2,21] Its structure (XXVIII) was elucidated in these Laboratories.[50]

* The configuration at $C_{(1)}$ and $C_{(10)}$ is probably the same as that of zingiberene.[48]

[43] L. H. Briggs and W. J. Taylor, *J. Chem. Soc.* 1338. (1947)
[44] M. E. Grimal, *C. R. Acad. Sci., Paris* **135**, 1057 (1902).
[45] R. O. Hellyer and H. H. G. McKern, *Aust. J. Chem.* **9**, 547 (1956).
[46] A. J. Birch, *J. Chem. Soc.* 715 (1953).
[47] M. D. Soffer, C. Steinhardt, G. Turner and M. E. Stebbins, *J. Amer. Chem. Soc.* **66**, 1520 (1944).
[48] D. Arigoni, O. Jeger, *Helv. Chim. Acta* **37**, 881 (1954).
[49] S. Katsura, *J. Chem. Soc. Japan* **63**, 1470 (1942).
[50] F. Šorm, K. Vereš and V. Herout, *Chem. Listy* **46**, 100 (1952).

The hydrocarbon calacorene, $C_{15}H_{20}$, was isolated from the same oil; and has structure (XXIX) or (XXX).[51]

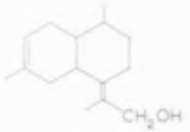
The *iso*cadinols $C_{15}H_{26}O$, which possess skeleton (I) but which do not afford cadinene dihydrochloride, include a crystalline alcohol of m.p. 75°, $[\alpha]_D^{20°}$: +3·7° from Bulgarian juniper oil. Khusol, isolated from vetiver oil, has the same skeleton but a different molecular formula ($C_{15}H_{24}O$); Bhattacharyya *et al.*[52] tentatively propose structure (XXXI) for it. Calameon, a sesquiterpenoid diol $C_{15}H_{24}O_2$, which has the skeleton (I), has been isolated from oil of calamus. It has structure (XXXII).[53]

XXVI

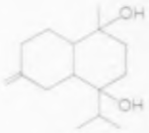
XXVII

XXVIII

XXIX resp. XXX



XXXI



XXXII

In this review we have attempted to survey the most important advances which have been made in this interesting group of sesquiterpenes. Even though the constitution and absolute configuration of a number of these compounds has been elucidated, a number of problems still await solution, particularly in connection with compounds having a cadinane skeleton and not yielding cadinene dihydrochloride.

[51] O. Motl, Private communciation.
[52] S. N. Dhingra, D. R. Dhingra and S. C. Bhattacharyya, *Perf. & Ess. Oil Rec.* 350 (1956).
[53] W. Treibs, *Ber. Dtsch. Chem. Ges.* **82,** 530 (1949).

Tetrahedron, 1958, Vol. 4, pp. 256–270. Pergamon Press Ltd., London

A STUDY OF THE ORIGIN AND MODIFICATIONS OF THE C_5 UNIT IN PLANT PRODUCTS—NEW SYNTHESIS OF ANGELICIN AND PSORALEN

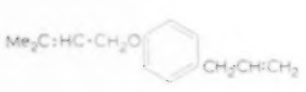
R. ANEJA, S. K. MUKERJEE and T. R. SESHADRI
Department of Chemistry, University of Delhi, Delhi

(*Received* 15 *May* 1958)

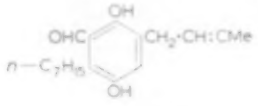
Abstract—A large number of natural essentially non-terpenoid compounds contain isoprene units. The C_5 units may have their origin based on senecioic acid, or mevalonic acid, but the fundamental stage seems to be an α-hydroxy-γ,γ-dimethylallyl system, which can undergo a number of modifications giving rise to types of compounds listed below under (A) to (F) in increasing order of complexity. The simpler furan derivatives are also now considered to be derived from C_5 units by the loss of three carbon atoms by oxidation. This is based not only on co-occurrence of types but also on the experimental feasibility of converting the dimethylallyl (C_5) and allyl groups into furans. In this connection, syntheses of angelicin and psoralen are described. Further the furan rings of furanoquinolines should be considered to have a similar origin.

AMONG natural products, a number of compounds are essentially non-terpenoid but have isoprene units present in them. Such compounds belong to diverse molecular types. The majority are components of higher plants, a few, however, are mould metabolic products. Their wide distribution has been noticed earlier.[1,2] Most of them are derivatives of benzopyrones though there are a number of examples which are derivatives of benzene, naphthalene and also of quinoline (see Tables 1 and 2).

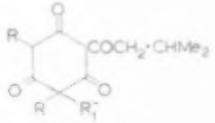
TABLE 1



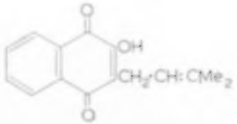
Foeniculin[51]



Flavoglaucin[52]



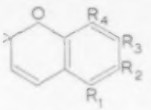
Lupulone[53], R—R_1
Humulone[53], R_1—OH
R—CH_2—CH:CMe_2



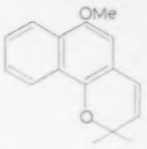
Lapachol[54]

[1] See T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18**, 77–244 (1952).
[2] See R. Robinson, *The Structural Relations of Natural Products*. Clarendon Press, Oxford, (1955).
[51] See T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18**, 82 (1952).
[52] A. Quilico and C. Cardani, *Gazz. Chim. Ital.* **83**, 1088 (1953).
[53] See T. J. Halsall, *Ann.* Reports. **49**, 190 (1952).
[54] S. C. Hooker, *J. Chem. Soc.* 1356 (1896); *J. Amer. Chem. Soc.* **58**, 1181 (1936).

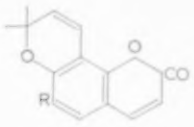
TABLE 2



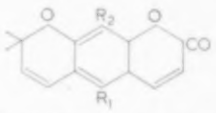
Evodione[55]; R_1=R_2=R_4=OMe, R_3=Acetyl
*allo*Evodione[57]; R_1=R_2=R_3=OMe, R_4=Acetyl
Evodionol[56]; R_1=OMe, R_2=Acetyl, R_3=OH, R_4=H.
*allo*Evodionol[57]; R_1=OMe, R_2=H, R_3=OH, R_4=Acetyl.
*allo*Evodionol methyl ether[56]; R_1=R_3=OMe, R_2=H, R_4=Acetyl



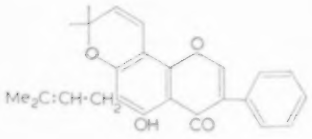
Lapachenol[58]



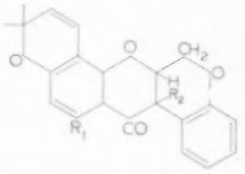
Seselin[59] (L); R=H
Braylin[20] (LI); R=OMe.



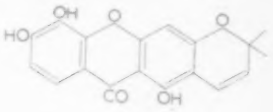
Xantylethin[60] (LII); R_1=R_2=H
Xanthoxyletin[61] (LIII); R_1=OMe, R_2=H
Luvangetin[62] (LIV); R_1=H, R_2=OMe



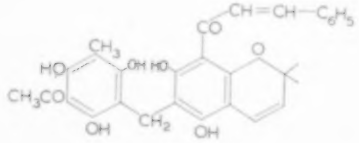
Osajin[63]; R=H
Pomiferin[63]; R=OH



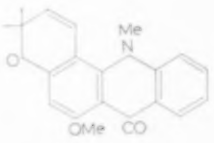
Deguelin[64] (LV); R_1=R_2=H
Toxicarol[64]; R_1=OH, R_2=H
Tephrosin[64]; R_1=R_2=OH.



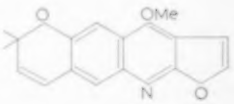
Jacareubin[65]



Rottlerin[65]



Acronycin[66]



Medicosmine[67]

[55] S. E. Wright, *J. Chem. Soc.* 2005 (1948).
[56] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 2376 (1950).
[57] K. D. Kirby and M. D. Sutherland, *Aust. J. Chem.* **9**, 411 (1956).
[58] R. Livingstone and M. C. Whiting, *J. Chem. Soc.* 3631, (1955).
[59] P. K. Bose, N. C. Guha, J. Matzke and E. Späth, *Ber. Dtsch. Chem. Ges.* **72**, 821 (1939).
[60] J. C. Bell and A. Robertson, *J. Chem. Soc.* 1828 (1936); J. C. Bell, A. Robertson and T. S. Subramaniam, *J. Chem. Soc.* 286 (1937).
[61] J. C. Bell, A. Robertson and T. S. Subramaniam, *J. Chem. Soc.* 627 (1936).
[62] P. K. Bose, E. Dobrovolny, A. Mookerjee, H. Schmid and E. Späth, *Ber. Dtsch. Chem. Ges.* **73**, 1361 (1940).
[63] W. L. Wolfrom, W. D. Harris, G. F. Johnson, J. E. Mahn, S. M. Moffet and B. Wildi, *J. Amer. Chem. Soc.* **68**, 406 (1946).
[64] See H. Haller, L. D. Goodhue and H. A. Jones, *Chem. Rev.* **30**, 33 (1942).
[65] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).
[66] L. J. Drummond and F. N. Lahey, *Aust. J. Sci. Res.* **A2**, 630 (1949).
[67] J. A. Lamberton and J. R. Price, *Aust. J. Sci. Res.* **6**, 173, (1953)
[68] A. McGookin, A. B. Percival and A. Robertson, *J. Chem. Soc.* 309 (1938); H. H. Brockmann and K. Maier, *Ann.* 535, 149 (1938); T. Backhouse, A. MacGookin, J. Machet, A. Robertson and E. Tittensor, *J. Chem. Soc.* 113 (1948).

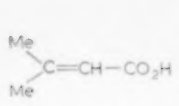
More than one C_5 unit is often present in a molecule. It may be linked to an oxygen atom forming an ether or to a nuclear carbon atom of the main skeleton. The unit has been encountered in several modifications differing in state of oxidation and also involved in ring formation by combination with an adjacent hydroxyl. Representative examples are given in the tables and also in the sequel, wherein a discussion of the evolution of various types is presented. Multiples of the C_5 unit, such as the geranyl group (C_{10}) and the farnesyl group (C_{15}), are also found. There seems to be adequate justification to consider that these C_5 units are introduced into the benzopyrone or other types at more or less the last stage. This is supported by the positions they occupy and the fact that frequently the unsubstituted nuclei occur along with the C_5-substituted compounds. In this respect there is considerable analogy with methylation including nuclear methylation.[3]

Origin

Various views have been expressed in the past regarding the origin of the C_5 unit, either present in larger terpene molecules or attached to aromatic nuclei. Geissman and Hinreiner[4] have adopted the earlier ideas that the C_5 is the result of condensation of C_2 and C_3. Recently, Robinson[5] has suggested senecioic acid (β,β-dimethylacrylic acid) (I) as the terpene precursor. Support for this scheme is provided by the experiments on the stimulation of rubber formation with senecioic acid in the guayule plant,[6] and *en bloc* incorporation of it into cholesterol[7] in rats, and pulegone[8] in *Mentha*. Robinson[5] considered the carboxyl of senecioic acid as the spearhead attacking aromatic nuclei.

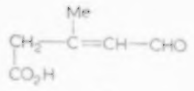
More recent work has emphasised the importance of mevalonic acid (β-hydroxy-β-methyl-δ-valerolactone)[9] (II) as a very likely intermediate in the biosynthesis of C_5 units in steroids,[10,11,12] carotenoids[13] and other terpenoid compounds.[14,15] The formation of C_5 isoprenoid units from this C_6 acid involves loss of a carbon atom by decarboxylation.[10] The dihydroxy acid from (II) may be considered to undergo initial oxidation of the primary alcoholic group to aldehyde and dehydration to produce a double bond, giving rise to (III).[15] Reaction of the aldehyde spearhead of (III) with an activated nuclear position of a phenolic compound (e.g. phloroglucinol) and decarboxylation would lead to the formation of (IV) which could be regarded as the primary stage, and from it various modified forms could be derived. An aldehyde grouping has been found to be an active spearhead, and further, recently aldehydes derived from the C_5 unit have been found to occur in nature.[16] It may be mentioned that in the study of nuclear methylation[3] in plant products, formaldehyde or its equivalent has been considered to be an active reagent.

[3] A. C. Jain and T. R. Seshadri, *Quart. Rev.* **10,** 169 (1956).
[4] T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18,** 229 (1952).
[5] R. Robinson, *The Structural Relations of Natural Products* p. 14. Clarendon Press, Oxford (1955).
[6] B. Arreguin, J. Bonner and B. J. Wood, *Arch. Biochem.* **31,** 234 (1951).
[7] K. Bloch, L. C. Clarke and I. Harry, *J. Amer. Chem. Soc.* **76,** 3859 (1954).
[8] W. Sanderman and H. Stockman, *Naturwissenschaften* **43,** 580 (1956).
[9] D. E. Wolff, C. H. Hoffmann, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *J. Amer. Chem. Soc.* **78,** 4499 (1956).
[10] P. A. Tavormina, M. H. Gibbs and J. H. Huff, *J. Amer. Chem. Soc.* **78,** 4498 (1956).
[11] F. Dituri, S. Gurin and J. L. Rabinowitz, *J. Amer. Chem. Soc.* **79,** 2650 (1957).
[12] O. Isler, R. Ruegg, J. Wursch, K. F. Gey and A. Pletscher, *Helv. Chim. Acta* **40,** 2369 (1957).
[13] G. D. Braithwaite and T. W. Goodwin, *Biochem. J.* **67,** 13P (1957).
[14] J. W. Cornforth, R. M. Cornforth, G. Popjak and I. Youhotsky-Gore, *Biochem. J.* **66,** 10P (1957).
[15] A. J. Birch, R. J. English, R. A. Massy-Westropp and H. Smith, *J. Chem. Soc.* 369 (1958).
[16] G. W. K. Cavill, D. L. Ford, H. Hinterberger and D. H. Solomon, *Chem. & Ind.* 292 (1958).

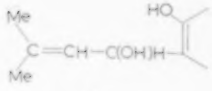


I

II



III

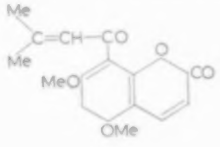


IV

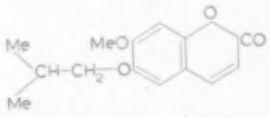
Other methods of deriving (IV) are possible, e.g. the senecioic acid hypothesis[5] will yield a ketone which could be considered to suffer selective reduction, but the aldehyde-acid (III) appears more convenient, particularly for building up multiple C_5 units. As a characteristic feature of (IV) may be mentioned its great capacity to undergo a number of changes. These points will be explained in the discussion of the typical examples given below.

Types

(A) *β,β-Dimethylacryl derivatives.* Probably the simplest modification of (IV) is represented by the β,β-dimethylacryl derivatives of coumarins, one example being glabra lactone[17] (V). Its formation requires a single step of oxidation of the secondary alcohol (IV) to the ketone(V). Closely related to this are the dihydro-compounds in which the *exo*cyclic double bond has undergone reduction, e.g. geigerin[18] (VI).



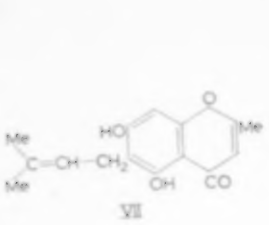
V



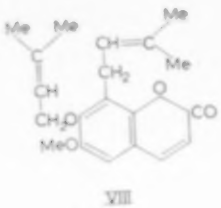
VI

(B) *γγ-Dimethylallyl group and its modifications.* In this type, the intermediate (IV) has undergone reduction, the —CHOH being converted into $—CH_2$, which seems to be fairly common and has been suggested as a biosynthetic step.[15] Peucenin[19] (VII) and brayleyanin[20] (VIII) are among the many known examples of this type. The double bond in the dimethylallyl group frequently gets oxidised forming either an epoxide as in auropten[21] (IX, R=CH_3), or a glycol, as in toddalolactone[22] (X, R=Me). These transformations have established laboratory analogies. It is interesting to record the simultaneous occurrence of both the oxidised (glabra lactone; V) and reduced (osthol; XI) forms of the precursor (IV) in *Angelica glabra* Makino.[17] Further, the dimethylallyl, the epoxide and the glycol types occur together linked to oxygen atoms of identical furanocoumarin structures (see Table IV).

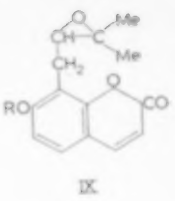
[17] K. Hata and A. Nita, *J. Pharm. Soc. Japan.* **77,** 941 (1957)
[18] F. N. Lahey and D. J. Wluka, *Aust. J. Chem.* **8,** 125 (1955).
[19] E. Späth and K. Eiter, *Ber. Dtsch. Chem. Ges.* **74,** 1851 (1941).
[20] F. A. L. Anet, G. K. Hughes and E. Ritchie, *Aust. J. Sci. Res.* A **2,** 608 (1949).
[21] H. Bohme and E. Schneider, *Ber. Dtsch. Chem. Ges.* **72,** 780 (1939).
[22] E. Späth, B. B. Dey and E. Tyray, *Ber. Dtsch. Chem. Ges.* **72,** 53 (1939).



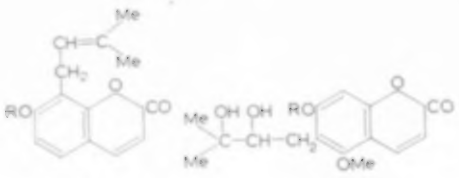
VII



VIII



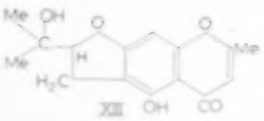
IX



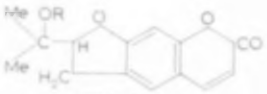
XI; R = OMe
XII; R = H

X

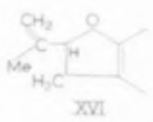
(C) *α-(β'-hydroxypyropyl)-dihydrofurans and α-isopropenyl-dihydrofurans.* Cyclisation of the epoxide (type IX, R═H) or the glycol (type X, R═H) with an adjacent phenolic hydroxyl can give rise to the dihydrofuran structure found in visamminol[23] (XIII) and marmesin[24] (XIV). Nodakenin[25] is a glucoside of the structure (XV) and on hydrolysis gives nodakenetin, a stereoisomer of (XIV). Loss of water leads to the modified structure, *iso*propenyl dihydrofuran (XVI), which is characteristic of rotenone[26] (XVII). These changes can be effected in the laboratory, e.g. 7-demethyl suberosin (XVIII) undergoes epoxidation and cyclisation to yield ± (XIV)[27]. The final dehydration, however, yields an isomeric *iso*propylfuran (XX) owing to the instability of the *iso*propenyl compounds in the presence of acids (compare isomerisation of rotenone into *iso*rotenone[28]).



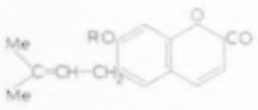
XIII



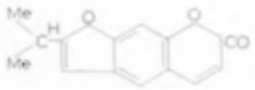
XIV; R═H
XV; R═Glc



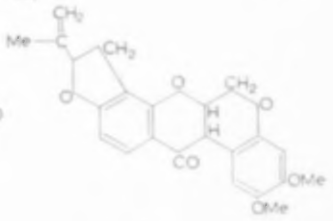
XVI



XVIII; R = H
XIX; R = Me



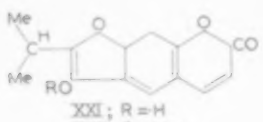
XX



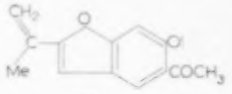
XVII

[23] W. Bencze, J. Eisenbeiss and H. Schmid, *Helv. Chem. Acta* **39**, 923 (1956).
[24] A. Chatterjee and S. S. Mitra, *J. Amer. Chem. Soc.* **71**, 606 (1949).
[25] E. Späth and E. Tyray, *Ber. Dtsch. Chem. Ges.* **72**, 2089 (1939).
[26] F. B. LaForge, H. L. Haller and L. E. Smith, *Chem. Rev.* **12**, 181 (1933).
[27] F. E. King, J. R. Housley and T. J. King, *J. Chem. Soc.* 1392 (1954).
[28] F. B. LaForge, H. L. Haller and L. E. Smith, *Chem. Rev.* **12**, 189 (1933).

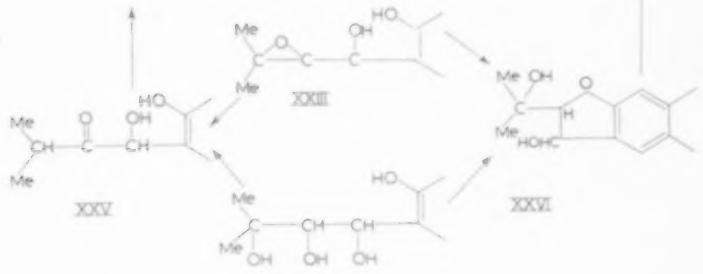
(D) α-iso*propyl-β-hydroxy-furans and relations*. As similar to type (C) but derived directly from the common precursor (IV) may be mentioned oreoselone[29] (XXI) and its methyl ether, peucedanin (XXII).[29] For their formation, it is suggested that (IV) is oxidised to the epoxide (XXIII) or the triol (XXIV). Rearrangement of the epoxide or dehydration of the triol yields a ketone (XXV) which is capable of cyclisation to (XXI). On the other hand, the epoxide (XXIII) or the triol (XXIV) can cyclise to form the dihydroxy-dihydrofuran derivative (XXVI) which is found in athamantin[30,31] (XXVII) as the di-ester of *iso*valeric acid. The dihydroxy structure (XXVI) can dehydrate to yield the type represented by euparin[32] (XXVIII). When athamantin is subjected to acid hydrolysis, it undergoes dehydration also to form oroselone[30,31,33] (XXIX).



XXI; R = H
XXII; R = Me

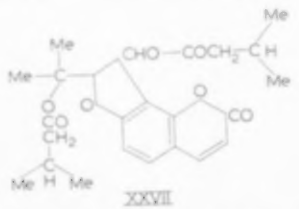


XXVIII

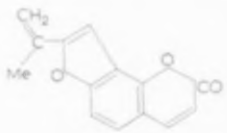


XXV XXIII XXIV XXVI

(E) 3-*Hydroxy*-iso*pentanyl derivatives*. This type involves a reduced form of an isomer (XXX), which is produced by the oxotropic rearrangement of the precursor (IV). Such an oxotropic change of 1-phenylallyl alcohols into cinnamyl alcohols[37] is well known. The simplest example is found in the flavonol glycoside icariin[34,35] (XXXI) which on hydrolysis yields the aglycone icaritin (XXXII). The ten-carbon fragment in the coumarin marmin[36] (XXXIII) is also based on the same pattern.



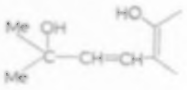
XXVII



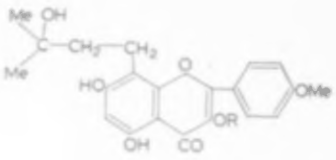
XXIX

[29] E. Späth, K. Klager and C. Schlösser, *Ber. Dtsch. Chem. Ges.* **64**, 2203 (1931).
[30] E. Späth and H. Schmid, *Ber. Dtsch. Chem. Ges.* **73**, 1309 (1940).
[31] H. Schmid, *Sci. Proc. Roy. Dublin Soc.* **27**, 145 (1956).
[32] B. Kamthong and A. Robertson, *J. Chem. Soc.* 933 (1939).
[33] E. Späth, N. Platzer and H. Schmid, *Ber. Dtsch. Chem. Ges.* **73**, 709 (1940).
[34] S. Akai, *J. Pharm. Soc. Japan* **55**, 537 (1935).
[35] S. Akai, M. Imaida and T. Matsukawa, *J. Pharm. Soc. Japan*, **55**, 214 (1935).
[36] A. Chatterjee and A. Choudhury, *Naturwissenschaften* **42**, 512 (1955).
[37] E. R. Braude, H. Jones and J. Stern, *J. Chem. Soc.* 396 (1946); 1087, (1947); See also E. R. Braude, *Quart. Rev.* **4**, 408 (1950).

(F) 2:2-*Dimethyl chromenes* (XXXIV) are very common and widely distributed. Many examples are available in different groups including benzene, naphthalene and benzopyrone derivatives (see Table 2). We consider that the oxotropic rearrangement of (IV), mentioned under (E), followed by ring closure with elimination of water, gives rise to 2:2-dimethyl chromenes. There seems to be no strict laboratory analogy for the ring closure but the structure of the tertiary alcohol (XXX) which is also allylic would be conducive to formation of the chromene ring.

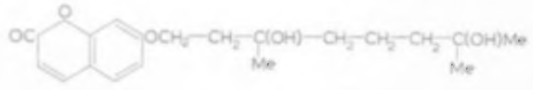


XXX



XXXI; R=Rhamno -glucose
XXXII; R=H

XXXIV



XXXIII

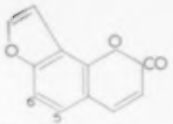
(G) *Simple furans:* In the types (A) to (F) above, the structural relations are fairly obvious, since all of them contain the C_5 unit. The biogenesis of unsubstituted furan structure (XXXV) has been far more difficult to understand. It is encountered mainly in the benzopyrone group and the furanocoumarins are the most numerous and the earliest known. However furano-derivatives of 2-methyl chromones and flavones are also well represented. In the furanoquinoline alkaloids the furan ring is found fused to the heterocyclic ring. The known examples are listed in Table 3. The furan ring present in all these groups seems to have similar biogenetic history.

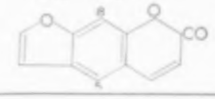
In his review of naturally occurring coumarins, Späth[38] enumerated compounds having the C_5 units and the furanocoumarins. He considered that the four carbon atoms of the furan ring along with one carbon atom of the central benzene ring could constitute an *iso*pentane unit as shown in (XXXVI). However, this is not consistent with his view of the origin of the benzene ring in simple coumarins and those carrying discreet *iso*pentane substituents; in these cases he preferred a carbohydrate origin for the benzene ring. In reviewing the same subject, Haworth[39] suggested that the unsubstituted furan rings of these natural coumarins were theoretically derivable by elimination of propane from a hypothetical α-*iso*propyl-dihydrofuran structure (XXXVII). Geissmann and Hinreiner[4] also examined the question. A two carbon phosphorylated keto alcohol moiety (XXXVIII) was suggested as the precursor and this was considered to cyclise to a furan-3-one (XXXIX) which subsequently yielded a furan ring by reduction and dehydration. It may be mentioned that this intermediate

[38] E. Späth, *Ber. Dtsch. Chem. Ges.* **70**, A83 (1937).
[39] R. D. Haworth, *Ann. Rep.* 344 (1937).

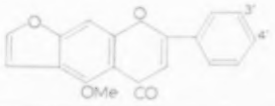
TABLE 3

Furanocoumarins

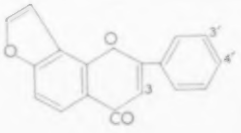


Name of compound	Substituents
Angelicin[44] (XLIII)	—
Sphondin[69]	6-OMe
*iso*Bergapten[70]	5-OMe
Pimpinellin[71]	5:6-$(OMe)_2$
Psoralene[46] (XLV)	—
Bergaptol[72]	5-OH
Bergapten[73] (LVI)	5-OMe
Xanthotoxol[74]	8-OH
Xanthotoxin[75] (LVII)	8-OMe
*iso*Pimpinellin[76] (LVIII)	5:8-$(OMe)_2$
8-Hydroxy bergapten[77] (LIX)	5-OMe-8-OH.
Prangenin[78]	8-O-Butyl
*iso*Imperatorin[79] (LX)	5-OCH_2—CH=CMe_2
Oxypeucedanin[80](LXI)	
Ostruthol[81] (LXII)	5-OCH_2—CH—CMe_2 5-OCH_2—CH—C(OH)Me_2 OCO—C(Me)=CHMe
Imperatorin[82] (LXIII)	8-OCH_2—CH=CMe_2
Phellopterin[83]	5-OMe-8-OCH_2—CH=CMe_2
Byakangelicol[84]	
Byakangelicin[84]	5-OMe-8-OCH_2—CH—CMe_2 OH OH
Bergamotin[85]	5-O-Geranyl
8-Geranyloxypsoralene[86]	8-O-Geranyl 

Furanoflavones



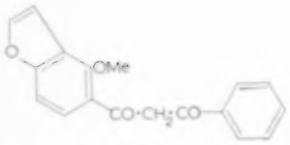
Name of compound	Substituents
Pinnatin[87]	—
Gamatin[87]	3′-4′-methylenedioxy



References for Table 3 on page 265

TABLE 3—*contd.*

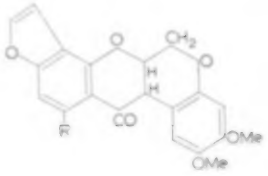
Name of compound	Substituents
Lanceolatin[88] B	—
Karanjin[89]	3-OMe
Pongapin[90]	3-OMe-3′:4′-methylenedioxy.



Pongamol[91]

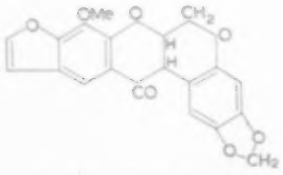
Furanochromones

Name of compound	Substituents
Visnagin[92] (LXIV)	2-Me-5-OMe
Khellin[93] (LXV)	2-Me-5:8-$(OMe)_2$
Khellinol[21] (LXVI)	2-Me-5-OH-8-OMe
Khellol glucoside[94] (LXVII)	2-CH_2O-Gl-5-OMe
Ammiol[95] (LXVIII)	2-CH_2OH-5:8-$(OMe)_2$



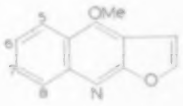
Rotenoids

Name of compound	Substituents
Elliptone[84] (LXIX)	R═H
Malaccol[44] (LXX)	R═OH



Pachyrrhizon[96] (LXXI)

Furanoquinolines



References for Table 3 on page 265

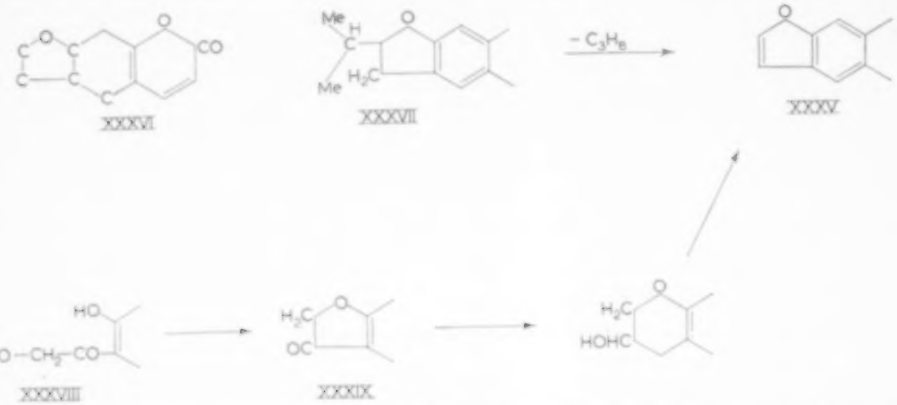
TABLE 3—*contd.*

Name of compound	Substituents
Dictamnine[97] (LXXII)	—
γ-Fagarine[98] LXXIII)	8-OMe
Evolitrine[99]	6-OMe
Skimmianine[100] (LXXIV)	7:8-$(OMe)_2$
Kokusaginine[101,102]	6:7-$(OMe)_2$
Maculosidine[50] (XLVII)	6:8-$(OMe)_2$
Acronycidine[103]	5:7:8-$(OMe)_3$
Maculin[50]	?-methylenedioxy.
Kakusagin[104]	?-methylenedioxy
Flindersiamine[105]	8-OMe-6:7-methylenedioxy
Evoxine[48] (LXII)	8-OMe-7-OCH_2—CH(OH)—CMe_2(OH)
Evolatine[106]	6-OMe-7-OCH_2—CH(OH)—CMe_2(OH)

REFERENCES FOR TABLE 3

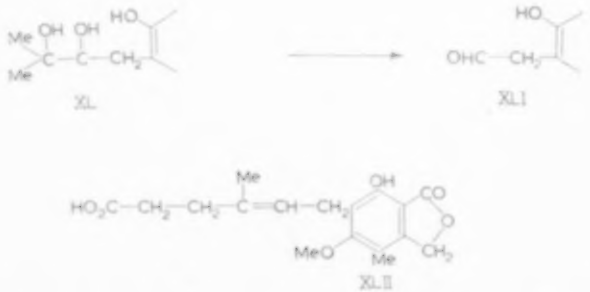
44 E. Späth and O. Pesta, *Ber. Dtsch. Chem. Ges.* **67,** 853 (1934).
46 E. Späth, B. L. Manjunath, M. Pailer and H. S. Jois, *Ber. Dtsch. Chem. Ges.* **72,** 1087 (1939).
69 E. Späth and H. Schmid, *Ber. Dtsch. Chem. Ges.* **74,** 595 (1941).
70 F. Wessely and E. Noddler, *Monatsh.* **60,** 141 (1932).
71 G. Heut, *Arch. Pharm.* 236, 162 (1898).
72 E. Späth and L. Socias, *Ber. Dtsch. Chem. Ges.* **67,** 59 (1934).
73 C. Pomeranz, *Monatsh.* **14,** 29 (1893).
74 E. Späth and F. Vierhapper, *Ber. Dtsch. Chem. Ges.* **70,** 248 (1937).
75 H. Thoms and E. Baetcke, *Ber. Dtsch. Chem. Ges.* **45,** 3705 (1912).
76 F. Wessely and F. Kallab, *Monatsh.* **59,** 161 (1932).
77 F. A. Kincle, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956).
78 G. V. Pigulevskŭ and G. A. Kuznetsova, *Zhur. Obshchei. Khim.* **23,** 1237 (1953).
79 E. Späth and L. Kahovic, *Ber. Dtsch. Chem. Ges.* **66** 1146 (1933).
80 E. Späth and K. Klager, *Ber. Dtsch. Chem. Ges.* **66,** 914 (1933).
81 E. Späth and F. Christiani, *Ber. Dtsch. Chem. Ges.* **66,** 1150 (1933).
82 E. Späth and H. Holzen, *Ber. Dtsch. Chem. Ges.* **66,** 1137 (1933).
83 See T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18,** 100 (1952).
84 T. Noguchi and M. Kawanami, *Ber. Dtsch. Chem. Ges.* **71,** 344 (1938); **71,** 1428 (1938); **72,** 483 (1939).
85 E. Späth and P. Kainrath, *Ber. Dtsch. Chem. Ges.*, **70,** 2272 (1937).
86 W. L. Stanley and S. H. Vannier, *J. Amer. Chem. Soc.* **79,** 3488 (1957).
87 S. K. Pavanram and L. R. Row, *Aust. J. Chem.* **9,** 132 (1956).
88 S. Rangaswami and B. V. R. Sastry, *Curr. Sci.* **24,** 13 (1955).
89 B. L. Manjunath, A. Seetharamiah and S. Siddapa, *Ber. Dtsch. Chem. Ges.* **72,** 93 (1939).
90 L. R. Row, *Aust. J. Sci. Res.* A **5,** 754 (1952).
91 S. Rangaswami, S. Narayanaswamy and T. R. Seshadri, *J. Chem. Soc.* 1871 (1954).
92 E. Späth and W. Gruber, *Ber. Dtsch. Chem. Ges.* **74,** 1492 (1941).
93 E. Späth and W. Gruber, *Ber. Dtsch. Chem. Ges.* **71,** 106 (1938).
94 E. Späth and W. Gruber, *Ber. Dtsch. Chem. Ges.* **74,** 1549, (1941).
95 G. Seitz, *Arch. Pharm. Berlin* **287,** 79 (1954).
96 H. Bickel and H. Schmid, *Helv. Chim. Acta* **36,** 664 (1953).
97 Y. Asahina, T. Ohta and M. Inubuse, *Ber. Dtsch. Chem. Ges.* **63,** 2045 (1930).
98 B. Berinzaghi, A. Muruzabal, R. Labriola and V. Deulofeu, *J. Org. Chem.* **10,** 181 (1945).
99 R. G. Cook and H. F. Haynes, *Aust. J. Chem.* **7,** 273 (1954).
100 Y. Asahina and M. Inubuse, *Ber. Dtsch. Chem. Ges.* **63,** 2052 (1930); T. Ohta and Y. Mori, *Pharm. Bull. (Japan)* **3,** 396 (1955).
101 R. F. C. Brown, *Aust. J. Chem.* **8,** 121 (1955).
102 M. Terasaka, T. Ohta and K. Narahasi, *J. Pharm. Soc. Japan*, **75,** 1040 (1955).
103 F. N. Lahey, J. A. Lamberton and J. R. Price, *Aust. J. Sci. Res.* **A3,** 155 (1950).
104 M. Terasaka, T. Ohta and K. Narahasi, *Pharm. Bull. (Japan)* **2,** 159 (1954).
105 F. A. L. Anet, P. T. Gilham, P. Gow, G. K. Hughes and E. Ritchie, *Aust. J. Sci. Res.* A **5,** 412, (1952).
106 R. G. Gell, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **8,** 114 (1955).

(XXXVIII) was considered to be capable of condensation with acetone or its equivalent to form the *iso*pentane skeletal unit. Recently, Robinson[40] has indicated a few possibilities for the origin of the furan ring in furanoquinolines but has emphasised the uncertainty of these routes in the absence of any good clues.



A review of natural products reveals the striking association of compounds having unsubstituted furan rings with those having obviously noticeable *iso*pentane units. A number of examples of their co-occurrence are available (see Table 4). A more important feature is that, frequently, definite *iso*pentane units and unsubstituted furan rings are found incorporated together in one compound. Based on this intimate association, it is now suggested that the structure (IV) from which all known types of *iso*pentane structures can be derived, is also the precursor of simple furan rings. The transformation of structure (IV) into the glycol (XL) was discussed earlier under type (B). Oxidative cleavage of the glycol would result in the loss of three carbon atoms leaving a residue of two as an acetaldehyde (XLI), cyclodehydration of which would form unsubstituted furans.

The uncyclised two carbon system like (XLI) has not so far been encountered among natural products, but the *iso*prenoid substituent in the mould metabolite mycophenolic acid[41] (XLII) provides an instance where one of the two double bonds in a ten-carbon geranyl side chain has been cleaved in the above fashion leaving a chain of seven. Oxidation of the terminal aldehyde has yielded the carboxylic acid.



[40] R. Robinson, *The Structural Relations of Natural Products* p. 94. Clarendon Press, Oxford (1955).
[41] J. H. Birkinshaw, H. Raistrick and D. J. Ross, *Biochem. J.* **50**, 630 (1952).

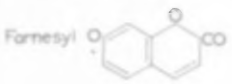
TABLE 4

Source	Constituents	Type
Angelica archangelica[107]	Umbelliprenin (LXXV)	C_{15}
	Osthol (XI)	C_5
	Angelicin (XLIII)	C_2
	Xanthotoxin (LVII)	C_2
	Imperatorin (LXIII)	C_2–C_5
Imperatoria Ostruthium[108]	Ostruthin (LXXVII)	C_{10}
	Osthol (XI)	C_5
	Imperatorin (LXIII)	C_2–C_5
	*iso*Imperatorin (LX)	C_2–C_5
	Oxypeucedanin (LXI)	C_2–C_5
	Ostruthol (LXII)	C_2–C_5–C_2
Luvanga scandens[109]	7-Methoxy-5-geranyloxy coumarin (LXXVI)	C_{10}
	Xanthyletin (LII)	C_5
	Luvangetin (LIV)	C_5
	Xanthotoxin (LVII)	C_2
	*iso*Pimpinellin (LVIII)	C_2
Zanthoxylum flavum[27]	Suberosin (XIX)	C_5
	Psoralene (XLV)	C_2
	Xanthotoxin (LVII)	C_2
Ammi visnaga	Visamminol[22] (XIII)	C_5
	Visnidin[110] (LXXVIII)	C_5
	Samidin[110] (LXXIX)	C_5
	Dihydrosamidin[110] (LXXX)	C_5
	Visnagin[92] (LXIV)	C_2
	Khellin[93] (LXV)	C_2
	Khellinol[31] (LXVI)	C_2
	Khellol glucoside[94] (LXVII)	C_2
	Ammiol[95] (LXVIII)	C_2
Derris elliptica[64]	Rotenone (XVII)	C_5
	Deguelin (LV)	C_5
	Elliptone (LXIX)	C_2
Pachyrrhizus erosus[96]	Rotenone (XVII)	C_5
	Pachyrrhizon (LXXI)	C_2
Zanthoxylum rhetsa[111]	Suberosin (XIX)	C_5
	Skimmianine (LXXIV)	C_2
Skimmia japonica[112]	Seselin (L)	C_5
	Skimmianine (LXXIV)	C_2

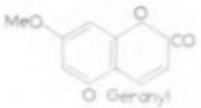
[107] E. Späth and F. Vierhapper, *Ber. Dtsch. Chem. Ges.* **71**, 1667 (1938).
[108] J. Herzeg and D. Krohn, *Arch. Pharm.* **247**, 553 (1909).
[109] P. K. Bose and A. Mookerjee, *J. Indian Chem. Soc.* **21**, 181 (1944).
[110] E. Smith, N. Hosanksky, W. G. Bywater and E. E. van Tamelen *J. Amer. Chem. Soc.* **79**, 3534, 1957; W. Bencze, O. Halpern and H. Schmid, *Experientia* **12**, 137 (1956).
[111] V. N. Gupta and T. R. Seshadri, *J. Sci. Ind. Res. (India)* **16C**, 71 (1957).
[112] Y. Asahina and M. Inubuse, *Ber. Dtsch. Chem. Ges.* **63**, 2052, (1930); E. Späth and O. Neufold, *Ber. Dtsch. Chem. Ges.* **71**, 353 (1938).

TABLE 4 (*contd.*)

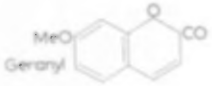
Source	Constituent	Types
Aegle marmelose[111]	Marmin[25] (XXXIII)	C_{10}
	Marmesin[24] (XIV)	C_5
	Imperatorin (LXIII)	C_2–C_5
	γ-Fagarine[114] (LXXIII)	C_5
Casimiroa edulis[77,115]	Bergapten (LVI)	C_5
	*iso*Pimpinellin (LVIII)	C_5
	8-Hydroxy bergapten (LIX)	C_5
	Dictamnine (LXXII)	C_5
	γ-Fargarine (LXXIII)	C_5
	Skimmianine (LXXIV)	C_5



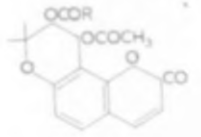
Umbelliprenin (LXXV)



7-Methoxy-5-geranyloxy coumarin (LXXVI)



Ostruthin (LXXVII)



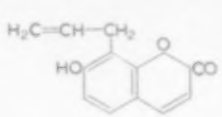
Visnidin[110] (LXXVIII); R—$CH(Me)C_2H_5$
Samidin[110] (LXXIX); R—$CH{:}CMe_2$
Dihydrosamidin[110] (LXXX); R—$CH_2.CHMe_2$

Support for the postulated biosynthetic route is provided by our recent work[42,43] on the synthesis of benzofuran derivatives, which has been based on these ideas. A facile laboratory synthesis for this group of natural products has been developed starting with *o*-hydroxy-allyl compounds. Cleavage of the allyl double bond has been effected by hydroxylation and subsequent fission of the glycol, or more directly by ozonolysis. The resulting acetaldehydes undergo ready *cyclo*dehydration to furans. For convenience, the work has been carried out with simple allyl derivatives instead of the γ,γ-dimethylallyl type, and the method has been shown to be workable for derivatives of benzene[42] chromone[42,43] and flavone.[42] Its successful extension to coumarins is reported in this paper; a new synthesis of angelicin[44] (XLIII) starting with 7-hydroxy-8-allyl coumarin[45] (XLIV) has been carried out.

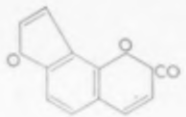
The use of simple allyl derivatives in these model experiments does not in any way detract from the argument in favour of biogenesis based on γ,γ-dimethylallyl

[42] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **2**, 203 (1958).
[43] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **2**, 203 (1958)
[45] B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **13**, 43 (1941).
[110] A Chatterjee, *Curr. Sci.* **12**, 209 (1943).
[114] K. K. Chakravarty, *J. Indian Chem. Soc.* **21**, 401 (1944).
[115] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).

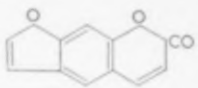
substituents. However, as a more appropriate example, the conversion of 7-hydroxy-6-dimethylallyl coumarin[27] (ex. Chloroxylon swietenia) (XVIII) into the furanocoumarin, psoralene[46] (XLV), is also described in the present communication. This is effected by ozonolysis and subsequent cyclisation of the product with phosphoric acid.



XLIV



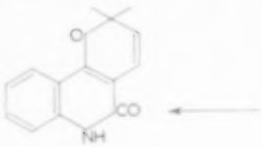
XLIII



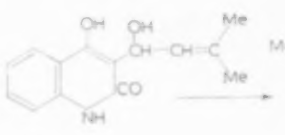
XLV

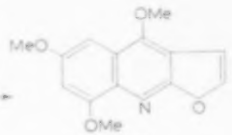
Furanoquinolines.

Since the furanoquinolines frequently occur along with the type of compounds discussed above, (see Table 4), there seems to be little doubt that the furan groups have, in this type also, the same origin. Further support is provided by the occurrence of flindersine[47] (XLVI) a pyranoquinoline and a number of furanoquinolines like maculosidine[48] (XLVII) in closely related *Flindersia* species. Another significant feature is the occurrence of furanoquinolines having *iso*pentane substituents in the same molecule, for example acronidine[49] (XLVIII) and evoxine[50] (XLIX). Hence the evolution of pyranoquinoline (XLVI) and furanoquinolines from a common precursor can be represented as given below.

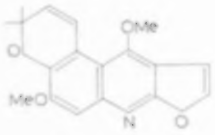


XLVI

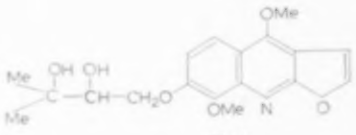




XLVII



XLVIII



XLIX

EXPERIMENTAL

7-Hydroxy coumarin-8-acetaldehyde. A stream of 2% ozonised oxygen (50 ml/min) was passed for 25 min through a cold solution (−5°) of 7-hydroxy-8-allyl coumarin[46] (XLIV) (200 mg) in dry ethyl acetate (30 ml). The solution was hydrogenated in the presence of 1% palladised charcoal (500 mg) till the rapid absorption of hydrogen ceased. The catalyst was then filtered and the filtrate evaporated to dryness. The residue was crystallised from ethyl acetate-hexane when the acetaldehyde (170 mg) was obtained as colourless short prisms, m.p. 140–41° (Found: C, 64·4; H 3·9; Calc. for $C_{11}H_8O_4$ C, 64·7; H, 3·9%). Its 2:4-dinitrophenylhydrazone crystallised from chloroform-methanol as light orange prisms m.p. 238–239°.

[47] R. F. C. Brown, J. J. Hobbs, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 348 (1954).
[48] R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 181 (1954).
[49] J. A. Lamberton and J. R. Price, *Aust. J. Chem.* **6**, 66 (1953).
[50] F. W. Eastwood, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 87 (1954).

Angelicin (XLIII). The acetaldehyde obtained above (100 mg) was dissolved in *ortho*-phosphoric acid (2 ml) and heated at 100° for 10 min. The solution was poured into water and the product extracted with benzene. The dried benzene solution was allowed to percolate through a short column of activated alumina and eluted with hexane. The eluate on evaporation yielded angelicin (90 mg). It crystallised from benzene–petroleum ether as colourless needles m.p. and mixed m.p. with an authentic sample, isolated from *Psoralea corylifolia*, 141–42°.

Conversion of 6-dimethylallyl-7-hydroxy-coumarin[27] (XVIII) *into psoralene*[46] (XLV). Ozonolysis of demethyl suberosin[27] (XVIII) (50 mg) was carried out as described in the above experiment, ozonised oxygen being passed for 7 min. After hydrogenation, the crude acetaldehydo-coumarin was cyclised by heating to 80° for 2 min with *ortho*-phosphoric acid (1 ml). The mixture was diluted with water and extracted with benzene. The dried benzene solution was allowed to percolate through a short column of activated alumina. The eluate on evaporation yielded psoralene (40 mg) crystallising as colourless needles from methanol, m.p. and mixed m.p. with an authentic sample isolated from *Psoralea corylifolia*, 161–62°.

Acknowledgement—Our grateful thanks are due to Prof. F. E. King for a gift of 7-demethyl suberosin.

Tetrahedron, 1958, Vol. 4, pp. 271–274. Pergamon Press Ltd., London

CONSTITUTION OF DALBERGIN—IV

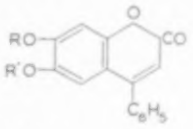
A NOVEL TRANSFORMATION OF O-METHYLDALBERGIN

V. K. AHLUWALIA, A. C. MEHTA and T. R. SESHADRI
Department of Chemistry, Delhi University, Delhi

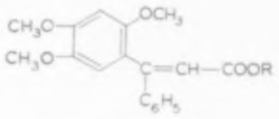
(*Received* 15 *May* 1958)

Abstract—O-methyldalbergin and related 4-phenylcoumarins are markedly different from ordinary coumarins in their behaviour towards alkali. They are stable in boiling alkali and on addition of mercuric oxide yield coumarilic acids. Phenyl-coumarilic acids undergo decarboxylation readily when boiled with aqueous alcoholic mercuric chloride to yield phenyl substituted coumarones.

IN part III[1] it was shown that dalbergin is 4-phenyl-6-hydroxy-7-methoxy-coumarin (I). O-methyldalbergin (II) was reported earlier[2] to be stable to boiling aqueous alkali and give an O-methyl ether of the corresponding cinnamic acid (III) which can be esterified to (IV) and demethylated to nordalbergin (V). According to Seshadri and co-workers,[3] mercuric chloride converts an *ortho*-methoxy *cis*-acid into the trans form, and as (III) is unchanged by mercuric chloride, it is considered to have the trans structure.

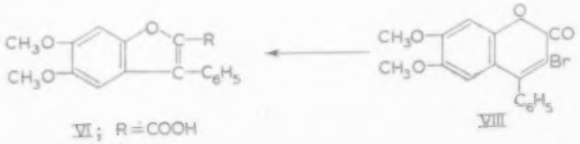


I; R = CH_3, R′ = H
II; R = R′ = CH_3
V; R = R′ = H



III; R = H
IV; R = CH_3

Attempts to prepare *ortho*-hydroxy *trans*-cinnamic acid from (II) gave unexpected results. Treatment of (II) with mercuric oxide in alkaline medium for a long period gives a non-phenolic acid, $C_{17}H_{14}O_5$, which may be decarboxylated to a non-phenolic neutral substance, $C_{16}H_{14}O_3$. As mercury is formed during the reaction, oxidation has taken place. This suggested that the acid is 3-phenyl-5:6-dimethoxycoumarone-2-carboxylic acid (VI) and the neutral substance 3-phenyl-5:6-dimethoxy-coumarone (VII).



VI; R = COOH
VII; R = H

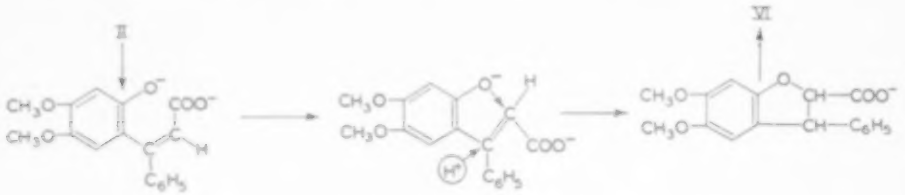
VIII

These conclusions were confirmed by comparison with authentic samples. (II) was monobrominated to (VIII) which when refluxed with aqueous alkali, formed

[1] V. K. Ahluwalia, A. C. Mehta and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **45**, 15 (1957).
[2] V. K. Ahluwalia and T. R. Seshadri, *J. Chem. Soc.* 970 (1957).
[3] S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **5**, 249 (1937).

3-phenyl-5:6-dimethoxycoumarone-2-carboxylic acid (VI). Decarboxylation with copper and quinoline gave the corresponding coumarone (VII).

Mercuric oxide is an efficient catalyst for *cis–trans* inversion of hydroxycinnamic acids derived from coumarins.[4] Coumarin, 6-nitro coumarin and 4-methyl-7-methoxy coumarin, yield only the corresponding coumaric acids (*trans*-cinnamic acids) by this treatment.[4,5] The transformation of (II) with mercuric oxide involves dehydrogenation which has also been observed in other 4-phenyl coumarins such as 4-phenyl-7-methoxy- and 4-phenyl-7:8-dimethoxy-coumarins, although the amount of conversion into coumarilic acids is much lower as compared with (II).



The formation of coumarilic acids from 4-phenylcoumarins may depend on the capacity of the α-carbon atom of the *trans*-cinnamic acid produced to develop a positive charge and the β-carbon atom a negative charge. This effect may be attributed to the combined influence of two phenyl groups as coumaric acids with one phenyl group alone do not undergo the change.

Decarboxylation in the presence of mercuric chloride has been observed in certain cases of furan α-carboxylic acids by Gilman and Wright[6] who came to the conclusion that this decarboxylation is of general utility for halogen and alkyl substituted 2-furoic acids. They found that the reaction failed with 5-nitro-2-furoic acid. Experiments carried out using coumarilic acids have not produced any marked decarboxylation, but with the phenyl-substituted coumarilic acids the decarboxylation is complete.

EXPERIMENTAL

3-Phenyl-5:6-dimethoxy-coumarone-2-carboxylic acid (VI)

(i) *Action of mercuric oxide and alkali on* O-*methyldalbergin.* O-methyldalbergin[1,2] (2 g) dissolved in hot aqueous potassium hydroxide (30 cm³, 20%) was diluted with water (70 cm³) and refluxed with freshly prepared yellow mercuric oxide (15 g) for 10 hr. The mixture was filtered, the filtrate saturated with hydrogen sulphide to remove mercury, filtered again and acidified. The acid product obtained was purified (sodium hydrogen carbonate) and crystallised from methanol; colourless rectangular plates (1·5 g), m.p. 224–225° (Found: C, 68·4; H, 5·1; $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%). It gave an orange red colour with alcoholic ferric chloride. Mixed m.p. with a sample prepared by method (ii) was undepressed.

(ii) 3-*Bromo*-4-*phenyl*-6:7-*dimethoxy-coumarin* (VIII). To a hot solution of O-methyldalbergin[1,2] (2·8 g) in glacial acetic acid (20 cm³) a solution of bromine in

[4] P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **3**, 293 (1936).
[5] K. S. Murty, P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **6**, 316 (1937).
[6] H. Gilman and G. F. Wright, *J. Amer. Chem. Soc.* **55**, 3303 (1933).

glacial acetic acid (16 cm^3; 10%) was added with shaking (10 min). Bromine was absorbed immediately and on cooling, colourless crystals (2·8 g) separated which crystallised from glacial acetic acid as colourless rectangular plates, m.p. 190–91°; diluting the mother liquor with water gave (0·2 g) more (Found: C, 56·4; H, 3·7; $C_{17}H_{13}O_4Br$ requires C, 56·5; H, 3·6%).

Action of alkali on the bromo-coumarin. The bromo compound (3 g) was refluxed with aqueous NaOH (150 cm^3; 10%) for 4 hr. The solution was cooled, the insoluble portion filtered, and the filtrate acidified with dilute hydrochloric acid. The product was purified by treatment with sodium hydrogen carbonate and it crystallised from methanol as colourless rectangular plates (1·9 g), m.p. 224–225°.

The *methyl ester* prepared from (VI) (obtained by both methods) by methylation with dimethyl sulphate, acetone and potassium carbonate or sodium bicarbonate crystallised from methanol as small colourless prisms, m.p. 135–36° (Found: C, 69·6; H, 5·3; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). It was insoluble in cold 5% sodium hydroxide and gave no colour with alcoholic ferric chloride. On hydrolysis it gave the original acid m.p. and mixed m.p. 224–25°.

3-*Phenyl*-5:6-*dimethoxy-coumarone* (VII)

(i) *Action of mercuric chloride on the coumarone-carboxylic acid.* (VI) (0·5 g) and mercuric chloride (1 g) were refluxed with aqueous alcohol (50 cc; 50%) for 6 hr. The solution was acidified with hydrochloric acid to make the strength 1%, and alcohol removed under reduced pressure and the residue extracted with ether. The ether solution was washed with aqueous sodium hydrogen carbonate and the solvent distilled. The residue (0·35 g) crystallised from methanol as clusters of colourless needles, m.p. 94–95°. Mixed m.p. with a sample prepared as given below (ii) was undepressed (Found: C, 75·5; H, 5·7; $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

(ii) *Decarboxylation of* (VII). 3-Phenyl-5:6-dimethoxy-coumarone-2-carboxylic acid (1 g) was heated at 220° in quinoline (10 cm^3) solution with copper powder (0·4 g) until the evolution of carbon dioxide ceased (30 min). The cooled mixture was poured into ether, the solution filtered and washed with dilute hydrochloric acid to remove quinoline and then with aqueous sodium hydrogen carbonate, dried and the solvent distilled. The viscous residue crystallised from methanol as clusters of colourless needles (0·8 g), m.p. 94–95°.

Methyl 2:4:5-*trimethoxy-β-phenylcinnamate* (IV) was prepared by heating (III)[2] with dimethyl sulphate and potassium carbonate in acetone for 3 hr. It crystallised from methanol as colourless rectangular plates, m.p. 92–94° (Found: C, 69·7; H, 5·9; $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

Action of hydriodic acid on 2:4:5-*trimethoxy-β-phenylcinnamic acid* (III)[2]. (III) (0·5 g) was refluxed with acetic anhydride (10 cc) and hydriodic acid (5 cm^3) for 2 hr. The mixture was poured into cold saturated aqueous sodium bisulphite (75 cm^3). The solid product was filtered and crystallised from ethyl acetate-petroleum ether mixture yielding colourless small rectangular plates and small prisms (0·3 g), m.p. 268–69°, undepressed by an authentic sample of nordalbergin (V).[1,2] The acetate and the methyl ether melted at 157–58° (O-acetyl nordalbergin) and 144–45° (O-methyldalbergin) respectively.

3-*Phenyl*-6-*methoxy-coumarilic acid*, prepared from 4-phenyl-7-methoxy-coumarin,[1] mercuric oxide and sodium hydroxide (20 hr refluxing) as in the case of (II) crystallised

from methanol as colourless plates and needles, m.p. and mixed m.p. with an authentic sample[7] 204–6°. Yield, 14%.

3-*Phenyl*-6-*methoxy-coumarone* obtained by the decarboxylation of the above acid either with mercuric chloride in aqueous alcoholic medium or with copper-quinoline, crystallised from petroleum ether as colourless needles, m.p. 41–42°. Motylewski[8] recorded the same m.p. for this product.

2:4-*Dimethoxy-β-phenyl-cinnamic acid*, prepared from 4-phenyl-7-methoxy-coumarin by the action of dimethyl sulphate and methanolic potash, crystallised from methanol as pale yellow plates, m.p. 170–71° (Found: C, 71·9; H, 6·0; $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%).

3-*Phenyl*-6:7-*dimethoxy-coumarilic acid* was prepared from 4-phenyl-7:8-dimethoxy-coumarin[2] by heating with mercuric oxide and sodium hydroxide solution; the acid crystallised from methanol as clusters of colourless needles, m.p. 196–198°. Yield 33% (Found: C, 69·0; H, 4·5; $C_{17}H_{14}O_5$ requires 68·4; H, 4·7%). Mixed m.p. with a sample prepared by the method given below was undepressed.

3-*Bromo*-4-*phenyl*-7:8-*dimethoxy coumarin*, prepared by bromination of 4-phenyl-7:8-dimethoxy-coumarin[2] in acetic acid medium, crystallised from hot glacial acetic acid as colourless rectangular plates and small prisms, m.p. 231–33° (Found; C, 57·0, H, 4·0; $C_{17}H_{13}O_4Br$ requires C, 56·5; H, 3·6%). It was refluxed with sodium hydroxide solution and the product, 3-*phenyl*-6:7-*dimethoxy-coumarilic acid* crystallised from methanol as colourless needles m.p. 196–198°.

3-*Phenyl*-6:7-*dimethoxy-coumarone*, obtained by decarboxylation of the above acid crystallised from alcohol as small colourless leaflets, m.p. 83–84°, as recorded previously.[8]

2:3:4-*Trimethoxy-β-phenyl-cinnamic acid*, prepared from 4-phenyl-7:8-dimethoxy-coumarin[2] crystallised from methanol as aggregates of small prisms, m.p. 168–70° (Found: C, 68·7; H, 5·8; $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%). The methyl ester crystallised from methanol as colourless prisms, m.p. 89–90° (Found: C, 70·0; H, 5·9; $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

Acknowledgement—We convey our thanks to the Council of Scientific and Industrial Research, India, for a research grant.

[7] T. R. Seshadri and S. Varadarajan, *J. Sci. Ind. Res.* (*India*) B **11**, 59 (1952).
[8] S. Motylewski, *Ber. Dtsch. Chem. Ges.* **42**, 3148 (1909).

Tetrahedron, 1958, Vol. 4, pp. 275–293. Pergamon Press Ltd., London

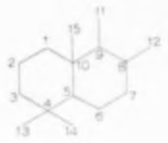
THE SESQUITERPENOID IRESIN

M. G. ROSSMANN and W. N. LIPSCOMB
School of Chemistry, University of Minnesota, Minneapolis 14, Minn.

(*Received* 19 *May* 1958)

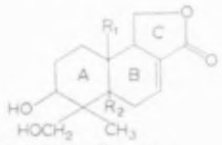
Abstract—The three-dimensional structure of the sesquiterpenoid iresin has been obtained from an X-ray diffraction study of the *p*-dibromobenzoate diester. The position of the angular methyl group is in agreement with the bi*cyclo*farnesol skeleton, previously found only in higher terpenes.

DJERASSI *et al.*[1] isolated a new tricyclic sesquiterpenoid $C_{15}H_{22}O_4$ from the Mexican plant "Iresine celosioides". This compound, named iresin, was shown to be tricyclic,[2,3] with the unique feature of possibly possessing the bi*cyclo*farnesol(I), or a closely related, skeleton. If so, iresin would be the "long-sought-after missing link"[2] between



I

the higher and lower terpenes: this skeleton is present in all diterpenes, triterpenes and steroids, and its absence in the lower terpenes has been taken to indicate a fundamental difference between the biogenesis of the lower terpenes and the higher terpenes. We shall show that iresin is in fact based on the bi*cyclo*farnesol skeleton.



IIa $R_1 = CH_3$ $R_2 = H$
IIb $R_1 = H$ $R_2 = CH_3$

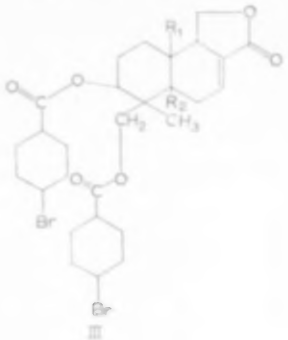
At the time we started, the detailed stereochemistry and position of the angular methyl group were unknown. Classical organic procedures had not decided between Structures (IIa) and (IIb), but the OH group on C-3, the carbon atom bearing the primary hydroxyl function, and the 5-6 bond were thought to be all *cis*. The present X-ray diffraction study has confirmed these aspects of stereochemistry, established the position of the methyl group, and established all three-dimensional aspects of

[1] C. Djerassi, P. Sengupta, J. Herran and F. Walls, *J. Amer. Chem. Soc.* **76**, 2966 (1954).
[2] C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, *J. Amer. Chem. Soc.* **76**, 6410 (1954).
[3] C. Djerassi and W. Rittel, *J. Amer. Chem. Soc.* **79**, 3528 (1957).

the molecular geometry except for the absolute configuration. Preliminary communications of the X-ray evidence[4] for the stereochemistry and presently available chemical evidence[5] for the stereochemistry and absolute configuration are in complete agreement.

EXPERIMENTAL DATA

A heavy atom derivative was prepared here by Dr. Paul Tomboulion who esterified the two OH groups by treating iresin with *p*-bromobenzoyl chloride in pyridine.



III

The product (III), recrystallized from a benzene-*cyclo*hexane mixture, melted at 211·5–212° (corrected). Infrared spectra of iresin and this derivative indicated no changes in the iresin residue other than esterification.

Very thin crystals about 0·5 × 0·5 mm² were grown from benzene solution over a period of a month. Equi-inclination Weissenberg photographs were taken of levels 0, 1, 2, 3 and 4 about the *b* and *c* axes with Cu$K\alpha$ radiation. The unit cell is monoclinic, with parameters $a = 28{\cdot}75$, $b = 7{\cdot}41$, $c = 6{\cdot}40$ Å. and $\beta = 92°$, where the *a* axis is perpendicular to the plate. Our measured density of 1·526 g cm^{-3} gives a molecular weight of 627 if two molecules are in the unit cell, in good agreement with the expected value of 632 for (III). The systematic absence only of $0k0$ when *k* is odd indicates either $P2_1$ or $P2_1/m$, but the molecule cannot be expected to have either a mirror plane or a centre of symmetry. Hence the space group $P2_1$, later shown to be correct, was assumed.

Visual estimates of 1432 independent diffraction maxima were made with the multiple film technique in which account was taken of the variation of film factor with angle of incidence.[6] The usual Lorentz-polarization corrections were made, and corrections for absorption were estimated only on those very few reflections for which the incident or diffracted ray passed in the plane of the plate-like crystal. The very thin background band was used to indicate the magnitude of the correction for these few reflections. The use of reflections common to the several films allowed correlation to a single scale, later made absolute by comparison with trial structures.

STRUCTURE DETERMINATION

The Patterson projection along *c* yielded the Br positions which were so close to $P2_1/m$ symmetry that the remainder of the structure was obscured by a pseudo-mirror

[4] M. G. Rossmann and W. N. Lipscomb, *J. Amer. Chem. Soc.* **80**, 2592 (1958).
[5] C. Djerassi, F. W. Donovan, S. Burstein and R. Mauli, *J. Amer. Chem. Soc.* **80**, 2593 (1958).
[6] M. G. Rossmann, *Acta Cryst.* **9**, 819 (1956).

plane. Hence, the three-dimensional Patterson function was computed with sharpened coefficients $[F_0^2/(\hat{f})^2]$ exp $[2(B - B^1)(\sin^2\theta/\lambda^2)]$, where $B - B^1$ was chosen as 1·0 Å^2 and $\hat{f} = \Sigma f_j/\Sigma Z_j$ in the usual notation. The only unusual features of the obvious Br···Br peaks were the elongation of the non-Harker peaks (Fig. 1) along y, interpreted as displacement of 0·14 A from the pseudo-mirror plane, and the elongation of the Harker peaks which later was found to be due to pronounced anisotropy of the thermal motion of the Br atoms.

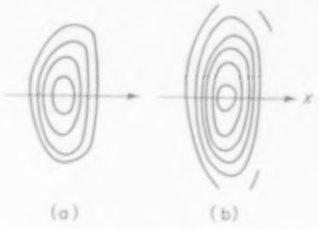


FIG. 1. (a) Single Br···Br Harker peak. (b) General double Br···Br peak. Contours are at 400 e^2/A^3.

The benzene rings were not obvious in the Patterson function, and hence only the positions of the Br atoms were used to compute phases for the first three-dimensional electron density map (F1). Had the Br atoms been placed exactly on the pseudo-mirror plane, the structure and its mirror image would have been superimposed, but the slight displacements of Br described above allowed the identification of the 7 C atoms (16–22) and O-1 and O-2 of one of the benzoate groups, as well as C-23, all of heights between 1 and 3 eA^{-3}. The effect of the pseudo-mirror plane was, however, still very evident. Four cycles of least-squares refinement of these atoms along with the Br atoms reduced $R = \Sigma|(|F_o| - |F_c|)|/\Sigma|F_o|$ from 0·62 to 0·41, an improvement due mostly to small changes in the Br positions and scale factor. During the last cycle of this refinement, the new phases were inserted into the computation of a new electron density map (F2).

Nearly all of the light atoms were found in F2. Those found above in F1, and therefore included in F2, had heights between 5 and 7 eA^{-3}, and those not yet introduced had heights between 1 and 3 eÅ^{-3}. A search was made for peaks at a distance of 1·5 Å, and at suitable bond angles from both the oxygen atoms that had so far been found. These peaks were marked and a similar search was then made of peaks 1·5 Å away from these, and so forth. At the same time the chemical reasonableness of the emerging structure was taken into account. In this way the molecule could be fitted to peaks in the Fourier without undue imagination except that atom C-9 did not correspond to any real peak and the bonds in the five-membered ring required a good deal of "stretching" (see Fig. 2). All other peaks in the map could be accounted for by the pseudo-mirror plane. These false peaks were generally slightly smaller in height, larger in area and of more irregular outline than the real peaks. Some atoms had no "mirror atom". There was general confusion where the second benzene ring might have been expected to turn up. Thus in the next trial structure the whole of the first benzoate group, as well as the iresin molecule itself and atoms O-4 and C-29, were included. Atom C-23 was omitted at this stage. A revision of the scattering

curve for Br had been made. Unfortunately this contained an error. It effectively reduced the light atom contributions to high-order planes by a factor of three but left the low-order planes unchanged in structure factors used for F2.

Two cycles of least-squares refinement, in which R fell from 0·38 to only 0·37, were carried out, and then the third electron density map, F3, was computed. Examination of F3 indicated that atom C-23 had been incorrectly placed in F1, and atoms O-4 and C-29 had been incorrectly placed in F2. Moreover, the second benzoate

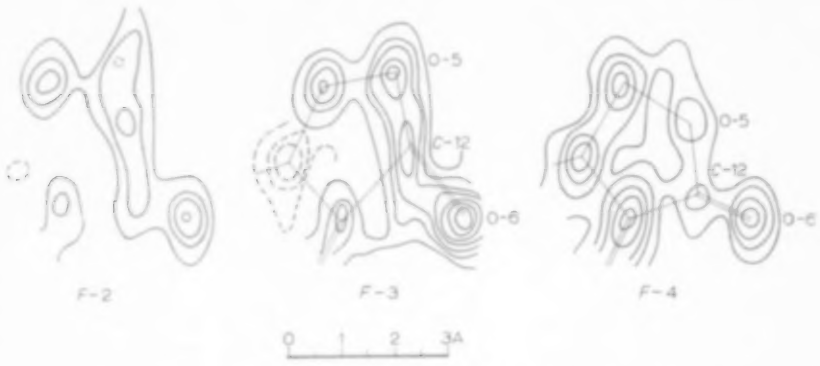


Fig. 2. Successive stages in determining the shape of the five-membered ring shown on section 14/20 c. Dotted lines show section 13/20 c and dashed line section 15/20 c. Contours are at intervals of 1 e/Å^3 upwards.

group was now clearly visible, but something was wrong with the five-membered ring. Atoms C-12 and O-5 (Fig. 2) did not give the expected well-resolved spherical peak, and the apparent temperature factor shifts indicated by least squares were unusually large. Therefore, only these two atoms were omitted from the next refinement. R was found to be 0·305. Computation of F4 only in the vicinity of the five-membered ring, with phases from all atoms except C-12 and O-5, showed clearly where these two atoms really were (Fig. 2), thus completing the structure. The difficulty had been caused by a "mirror peak" in F2 which was actually higher than the true peak.

REFINEMENT OF THE STRUCTURE

All atoms but hydrogen had been located, and hence three-dimensional least-squares refinement was tried but R fell only from 0·280 to 0·277 in three cycles. In an attempt to interpret this result, a three-dimensional difference electron density map D1 was computed. This map showed no variations higher than $\pm 2{\cdot}0$ eÅ^{-3}, all of which could be interpreted as shifts of light atoms, except for peaks up to 3·5 eÅ^{-3} around both bromines, indicating strong anisotropic thermal motion (Fig. 3). Six further cycles of least-squares refinement in which six thermal parameters were introduced for each of the two bromines, produced values of $R = 0{\cdot}182$ and $r = \Sigma\omega(|F_o|^2 - |F_c|^2)^2/\Sigma\omega F_o^4 = 0{\cdot}183$. The final electron density map F5 was now computed, composite sections of which are shown in Fig. 4. Except for a very few small peaks as high as 1·5 eÅ^{-3}, the background was below 1 eÅ^{-3}. Another three-dimensional difference electron density map D2 was also computed, which indicated

that the apparent thermal motions and termination of series effects around Br had been well accounted for (Fig. 3). This difference map showed no peaks higher than 1·6 eÅ^{-3}, but many peaks occurred at a height of about 1 eÅ^{-3}. When the expected parameters for hydrogen atom positions were evaluated, about three-fourths of these atoms fell on peaks greater than 1 eÅ^{-3}.

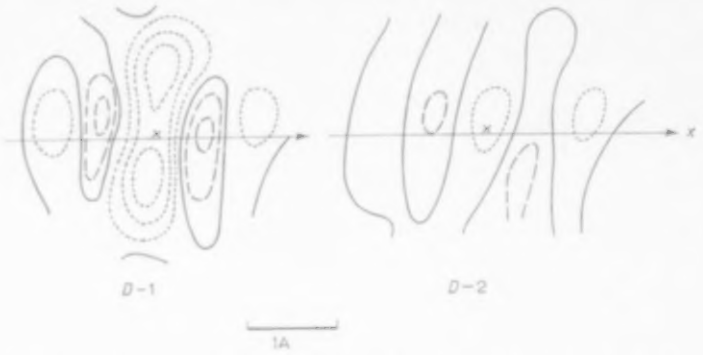


FIG. 3. Difference maps cut at 9/20 c. showing anisotropic motion of Br-2. Contours intervals of 1 e/A^3. Dashed lines are negative and dotted lines are positive contours.

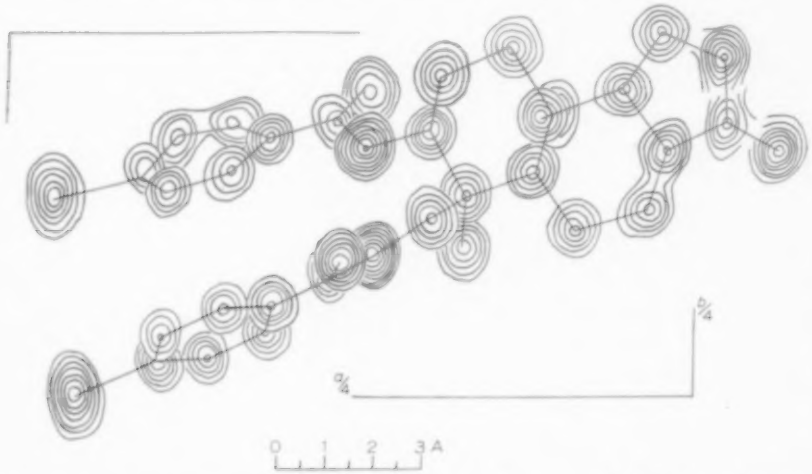


FIG. 4. Final electron density map. Contours are at intervals of 1 e/A^3 (except near bromines). The lowest contour is at a height of 2 e/A^3. Contours around bromines are at intervals of 5 e/A^3 upwards.

Further refinement of the structure is thus surely possible. The introduction of hydrogen atoms and possibly of anisotropic thermal parameters for other atoms than Br, especially atom O-3, would no doubt improve the already satisfactory agreement. In lieu of a complete table of the 1430 reflections, the agreement for different classes[7] of reflections is shown in Table 1. As a further check of the structure, a detailed examination was made of the 113 planes in Columns *a* and *b* of Table 1. Due to an error, we discovered that five of these planes, all having large indices, had

[7] R. E. Dickerson, P. J. Wheatley, P. A. Howell and W. N. Lipscomb, *J. Chem. Phys.* 27, 200 (1957).

been entered with either a wrong power of 10 or of 2 into the observed structure factor list used for refinements. However, the weighting factors for these five planes were small in the least-squares treatment, and we have shown that the maximum

TABLE 1. AGREEMENT FACTOR R FOR ALL CLASSES OF REFLECTIONS[a]

Class	R	n	a	b
All	0·182	1430	94	19
$0kl$	0·143	29	2	0
$h0l$	0·207	268	31	2
$hk0$	0·175	186	9	6
h odd	0·178	719	42	10
k odd	0·167	649	28	12
l odd	0·171	680	46	7
$h + k$ odd	0·180	710	42	10
$k + l$ odd	0·192	731	46	11
$h + l$ odd	0·180	721	54	13
$h + k + l$ odd	0·172	694	42	9

[a] Two reflections were outside the range of $\sin\theta$ for which computations were made. The number of reflections in each class is n. The number of planes showing $|F_o| > 2|F_c|$ is in Column a, and the number showing $|F_o| < (\frac{1}{2})|F_c|$ is in column b.

effect on the electron density maps is less than 0·2 eÅ^{-3}, even in the unlikely event that the errors are all at their maximum at a given point. Hence the effect of these errors is negligible, and their correction reduces R to 0·176. As an additional check on the over-all agreement, we have listed R as the scattering angle increases (Table 2).

TABLE 2. VARIATION OF R WITH $\sin\theta$

Range of $\sin\theta$	R	n	$\Sigma\|F_o\|$
0·00–0·15	0·249	14	606
0·15–0·30	0·136	91	4741
0·30–0·45	0·132	208	7283
0·45–0·60	0·140	361	7635
0·60–0·75	0·242	409	6574
0·75–0·90	0·244	242	2923
0·90–1·00	0·278	100	903

The five incorrectly listed planes were omitted. A final refinement in which all hydrogen atoms were included except those of the two methyl groups led to values of $R = 0{\cdot}163$ and $r = 0{\cdot}157$ and decreased the numbers in columns a and b of Table 1 by about a factor of two.

Isotropic temperature factor constants B in the formula $\exp(-B\sin^2\theta/\lambda^2)$ are shown in Fig. 7 for each atom. We have previously observed large least-square increases of B for atoms incorrectly placed in the structure[8] at early stages of the

[8] F. L. Hirshfeld, K. Eriks, R. E. Dickerson, E. L. Lippert, Jr. and W. N. Lipscomb, *J. Chem. Phys.* **28**, 56 (1958).

TABLE 3. CO-ORDINATES OF ATOMS IN 1 MOLECULE

Atom	*x/a*	*y/b*	*z/c*
Br-1	0·0318	0·0445	0·0274
Br-2	0·0507	0·4981	0·4427
C-1	0·3621	0·4561	0·5750
C-2	0·3096	0·3831	0·5504
C-3	0·3047	0·2312	0·4213
C-4	0·3301	0·0463	0·5190
C-5	0·3802	0·1158	0·5619
C-6	0·4105	0·9669	0·6603
C-7	0·4616	0·0127	0·7006
C-8	0·4738	0·1783	0·7002
C-9	0·4420	0·3465	0·6312
C-10	0·3915	0·2704	0·6824
C-11	0·4711	0·5038	0·7610
C-12	0·5210	0·2607	0·7655
C-13	0·3039	−0·0163	0·7209
C-14	0·3288	0·8996	0·3514
C-15	0·3857	0·2563	0·9257
C-16	0·0961	0·1007	0·0716
C-17	0·1140	0·0627	0·2924
C-18	0·1600	0·1192	0·3204
C-19	0·1873	0·2145	0·1579
C-20	0·1670	0·2416	−0·0253
C-21	0·1213	0·2226	−0·0471
C-22	0·2361	0·2631	0·1832
C-23	0·1101	0·6021	0·5485
C-24	0·1458	0·5978	0·4290
C-25	0·1884	0·6902	0·4962
C-26	0·1917	0·7543	0·6983
C-27	0·1556	0·7445	0·8273
C-28	0·1131	0·6716	0·7611
C-29	0·2342	0·8291	0·7784
O-1	0·2560	0·1850	0·3759
O-2	0·2592	0·3427	0·0611
O-3	0·2409	0·8611	0·9749
O-4	0·2630	0·8842	0·6400
O-5	0·5188	0·4308	0·7802
O-6	0·5586	0·1735	0·7956

refinement. In the present study we found that for atoms placed between 0·15 and 0·35 Å from their correct positions, the square of the full shift in temperature factor is roughly proportional to the full shift in position. Thus our earlier experience, that the behavior of temperature factors is a method of picking out incorrectly placed atoms, has been confirmed.

A list of co-ordinates for atoms in one molecule is given in Table 3. The observed amplitudes of scattering are listed in Table 4.

TABLE 4. OBSERVED STRUCTURE FACTORS ON ABSOLUTE SCALE

(*h*0*l*)

	l = 5	*l* = 4	*l* = 3	*l* = 2	*l* = 1	*l* = 0	*l* = 1	*l* = 2	*l* = 3	*l* = 4	*l* = 5
h = 0	21·7	24·3	38·2	51·6	68·1	(640·0)	68·1	51·6	38·2	24·3	21·7
1	—	—	—	144·7	34·4	(cut off)	78·4	146·1	21·7	21·9	20·1
2	23·0	23·3	38·1	63·6	86·8	32·4	39·2	105·6	44·3	20·4	20·1
3	23·0	23·3	16·5	129·3	45·4	14·8	26·5	122·4	13·6	5·6	—
4	29·3	28·2	55·8	47·6	77·7	45·5	11·5	42·5	27·0	6·3	20·3
5	31·7	28·3	50·2	72·2	67·9	21·6	25·1	13·8	34·0	27·2	20·3
6	28·5	19·0	8·0	20·0	17·9	4·0	23·2	7·3	35·3	23·5	20·6
7	23·3	26·7	56·7	21·6	56·6	4·5	13·9	—	9·2	8·0	—
8	23·6	—	42·3	39·8	71·0	16·5	68·8	—	5·6	8·6	20·9
9	—	—	—	52·0	37·8	68·8	15·3	52·6	15·4	—	—
10	—	23·0	—	50·9	23·9	84·3	14·1	41·6	16·1	18·2	—
11	—	17·6	7·1	7·0	18·2	54·3	60·7	101·7	10·3	18·8	—
12	—	6·8	—	28·2	17·0	63·4	7·6	90·7	12·6	46·8	—
13	—	10·0	10·8	21·6	7·6	44·4	17·0	94·9	6·2	21·7	—
14	—	4·9	37·6	23·0	29·9	140·0	12·4	55·2	9·2	48·9	—
15	—	5·2	8·9	19·4	38·7	47·8	58·8	51·9	6·9	36·4	29·3
16	—	5·4	20·4	18·8	52·3	17·7	43·5	24·2	20·6	29·6	20·3
17	—	11·7	25·6	9·5	27·5	10·9	47·3	53·9	7·3	14·7	28·2
18	—	8·5	21·7	—	50·4	11·4	25·6	—	16·5	—	27·6
19	—	—	27·8	8·7	44·9	26·1	77·2	—	22·2	10·9	26·8
20	—	—	—	—	54·5	23·2	28·9	21·7	15·8	17·2	—
21	—	6·1	29·2	15·5	16·7	23·9	43·5	18·7	25·0	25·8	—
22	—	12·7	—	—	28·2	8·0	22·0	48·5	25·1	—	—
23	—	15·2	10·1	—	—	13·2	20·8	8·3	—	17·2	—
24	—	15·1	18·9	—	—	12·5	—	35·8	7·8	16·6	—
25	—	5·4	—	29·7	29·9	7·7	—	19·1	—	22·7	—
26	—	8·6	—	14·1	16·7	7·7	—	22·2	7·5	21·4	—
27	—	7·1	—	16·1	—	15·7	19·1	10·1	7·2	14·0	—
28	—	—	9·7	—	24·1	11·0	21·3	16·7	8·7	12·7	—
29	—	—	—	8·3	23·4	—	27·7	14·7	11·4	7·5	—
30	—	—	—	—	20·1	—	32·0	—	21·5	8·9	—
31	—	—	11·5	—	12·4	—	29·6	—	12·3	—	—
32	—	—	9·4	8·1	12·7	—	28·7	—	16·2	—	—
33	—	—	—	—	11·5	—	21·7	—	3·4	—	—
34	—	—	—	7·0	9·1	9·8	20·3	4·1	—	—	—
35	—	—	—	—	—	—	12·7	—	—	—	—
36	—	—	—	—	—	14·5	6·9	—	—	—	—

(*h*1*l*)

h = 0	16·6	15·2	17·5	44·5	20·6	—	20·6	44·5	17·5	15·2	16·6
1	—	30·0	48·4	69·0	60·0	58·0	90·3	37·5	20·9	33·3	—
2	—	17·5	30·3	70·1	150·6	38·1	94·9	56·0	18·4	19·0	16·8
3	16·6	9·0	29·6	29·7	114·0	33·8	73·9	37·8	47·4	29·5	—
4	14·0	14·8	54·9	41·9	102·3	34·6	64·3	27·4	30·7	30·7	17·0
5	—	18·9	35·6	9·9	106·4	1·0	69·1	28·8	54·6	21·9	14·2
6	16·8	8·3	3·9	42·2	67·2	22·3	115·2	17·1	36·8	7·9	14·4
7	—	19·3	6·9	37·6	85·1	10·1	70·7	20·2	45·7	12·3	—
8	—	18·3	30·4	34·7	24·1	37·4	88·4	13·0	30·7	19·7	—
9	—	19·0	22·5	67·5	25·6	28·8	74·8	30·0	52·1	—	—
10	—	23·8	5·8	50·2	16·7	41·5	67·6	22·2	38·5	11·1	—
11	—	20·3	13·9	42·1	18·2	45·5	45·6	12·4	26·4	13·4	—
12	—	9·9	11·5	57·2	7·4	30·0	54·5	20·3	17·6	16·9	—
13	—	10·3	8·7	47·0	31·5	87·0	36·1	26·0	13·4	17·2	—
14	—	14·4	12·5	49·0	9·6	37·0	39·0	28·8	8·7	7·2	—
15	—	12·4	9·5	11·0	10·5	46·1	39·7	25·9	32·1	12·7	—
16	—	—	6·6	33·0	36·3	22·8	65·7	24·0	26·8	8·3	—
17	—	13·4	10·3	—	19·1	15·3	33·9	—	28·1	26·2	—
18	—	16·4	14·5	18·8	16·5	—	33·0	22·8	36·5	23·1	—

Table 4 (Cont'd.).

(h1l) contd.

	$l=\bar{5}$	$l=\bar{4}$	$l=\bar{3}$	$l=\bar{2}$	$l=\bar{1}$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$	$l=5$
$h=19$	—	8·3	7·3	21·0	19·8	—	40·9	12·2	39·3	8·6	—
20	—	12·0	15·4	29·2	15·5	25·9	42·1	24·0	10·3	8·6	—
21	—	13·3	15·8	37·3	—	36·0	27·0	24·3	24·6	12·5	—
22	—	—	11·7	27·5	16·0	39·9	22·5	17·7	23·9	—	—
23	—	13·1	16·2	35·8	18·4	49·0	26·8	34·4	13·6	8·2	—
24	—	—	8·0	26·2	—	40·3	11·7	29·5	13·4	11·0	—
25	—	—	—	13·6	19·8	20·6	15·8	33·5	9·8	5·8	—
26	—	—	12·3	16·2	28·0	28·8	10·5	24·3	9·5	9·2	—
27	—	—	10·0	22·3	12·9	14·5	—	30·4	7·0	9·2	—
28	—	—	9·7	—	17·9	16·6	—	23·0	8·6	8·3	—
29	—	—	12·8	8·3	9·6	12·7	—	11·6	10·8	7·2	—
30	—	—	12·2	—	9·8	10·5	—	8·3	13·4	—	—
31	—	—	10·0	—	11·5	6·3	—	—	8·1	—	—
32	—	—	9·2	—	9·8	8·5	—	9·2	9·8	—	—
33	—	—	—	7·2	7·6	5·6	—	8·1	4·2	—	—
34	—	—	—	—	—	14·5	—	19·3	—	—	—
35	—	—	—	—	—	14·5	6·7	—	—	—	—
36	—	—	—	—	—	10·9	—	—	—	—	—

(h2l)

	$l=\bar{4}$	$l=3$	$l=\bar{2}$	$l=\bar{1}$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$	$l=5$
$h=0$	17·1	11·7	54·2	50·9	44·7	50·9	54·2	11·7	17·1	—
1	17·3	27·5	77·4	49·0	87·0	26·5	61·8	16·1	11·8	—
2	—	33·9	34·1	77·7	104·8	60·7	67·6	31·8	17·9	—
3	21·3	36·7	42·8	47·8	92·9	56·2	56·9	38·2	16·9	21·3
4	8·2	26·4	28·3	56·9	45·2	38·0	25·9	10·9	24·0	—
5	21·9	41·5	—	16·7	22·7	48·0	70·8	25·0	13·1	—
6	13·1	26·1	56·8	57·6	29·6	19·8	17·6	23·2	—	—
7	—	43·5	45·9	21·5	30·6	35·9	24·0	27·0	25·5	21·7
8	6·9	14·0	35·8	33·5	38·5	64·3	46·2	22·2	14·5	21·7
9	9·6	22·6	23·4	30·8	26·5	26·1	40·5	22·8	6·5	21·7
10	4·7	8·4	40·9	37·8	52·1	32·7	48·5	—	16·8	21·7
11	15·5	6·7	21·9	31·3	61·4	21·3	60·6	17·9	21·6	—
12	—	20·3	19·0	6·9	63·1	28·4	45·7	15·8	24·4	—
13	10·4	15·3	11·5	25·3	41·5	13·6	61·8	12·2	24·8	—
14	—	—	—	26·1	24·7	15·8	41·3	—	22·7	—
15	—	22·2	—	25·8	25·8	18·2	33·5	21·4	—	—
16	—	22·8	21·9	27·0	32·8	31·1	27·2	13·6	13·1	—
17	12·3	19·3	22·5	45·4	15·1	26·3	32·1	13·9	25·9	—
18	5·2	22·9	—	47·3	—	39·0	24·9	24·0	9·4	—
19	8·0	13·6	13·6	28·7	18·1	59·5	27·7	27·8	12·7	—
20	10·2	11·5	31·1	37·0	—	19·1	—	—	13·1	—
21	—	10·1	14·2	19·6	—	40·2	38·9	8·0	13·0	—
22	8·2	10·3	28·3	12·7	19·0	27·0	33·0	8·0	8·2	—
23	8·9	14·2	20·2	12·9	—	10·0	24·8	14·0	15·7	—
24	—	—	16·2	15·1	16·1	—	9·9	9·4	21·3	—
25	12·5	—	—	—	—	—	25·4	—	14·2	—
26	—	13·7	17·9	15·1	12·0	10·5	12·7	—	9·3	—
27	8·2	9·0	—	18·2	11·9	14·1	24·6	7·3	19·0	—
28	—	—	7·7	17·7	11·7	15·1	23·6	8·1	16·8	—
29	—	6·9	—	24·1	—	15·1	8·4	15·0	—	—
30	—	7·3	—	13·4	—	25·6	6·4	9·5	—	—
31	—	5·9	—	12·7	—	22·5	9·5	10·6	—	—
32	—	—	—	18·6	7·0	20·6	—	11·9	—	—
33	—	—	6·4	—	—	17·7	—	—	—	—
34	—	—	—	—	—	6·0	—	—	—	—
35	—	—	—	—	7·8	—	—	—	—	—

Table 4 (Cont'd.).

(*h3l*)

	$l=5$	$l=4$	$l=3$	$l=2$	$l=1$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$	$l=5$
$h=0$	17·0	33·7	13·7	58·9	15·3	—	15·3	58·9	13·7	33·7	17·0
1	17·0	20·3	23·9	15·0	26·5	16·5	9·6	6·6	—	33·8	18·6
2	17·0	4·2	20·7	26·2	—	28·7	46·4	33·1	32·6	9·3	—
3	17·0	13·0	23·9	50·3	35·9	25·2	19·4	44·4	25·7	10·4	—
4	—	15·1	21·7	53·4	48·3	26·7	77·9	23·1	—	24·7	—
5	—	6·8	12·3	23·9	62·4	14·8	62·4	23·6	26·5	20·4	—
6	—	—	24·0	33·2	44·7	33·5	65·0	47·6	27·8	9·9	—
7	—	10·6	12·6	23·9	30·1	40·0	39·2	24·9	31·8	20·4	—
8	—	8·0	9·0	19·4	23·9	14·1	99·7	19·4	36·5	23·5	—
9	—	13·1	9·4	15·1	32·7	21·3	71·2	18·5	11·9	17·3	—
10	—	8·5	—	27·4	17·2	34·3	44·9	32·9	24·8	12·0	—
11	—	13·7	13·4	34·0	17·0	35·4	22·9	15·0	36·8	9·0	—
12	—	14·0	12·9	22·0	16·3	45·8	19·8	19·1	26·2	—	—
13	—	18·6	10·3	29·5	19·4	16·8	20·1	27·2	17·0	23·5	—
14	—	—	10·6	14·5	23·7	35·6	16·5	14·4	—	23·8	—
15	—	—	7·3	21·6	12·9	15·8	22·2	15·9	—	17·2	—
16	—	—	—	—	9·1	25·1	21·7	25·9	15·3	—	—
17	—	—	—	10·7	—	—	22·5	15·9	24·0	9·4	—
18	—	—	10·0	—	25·3	—	30·6	14·4	17·3	10·0	—
19	—	7·6	—	—	21·0	—	28·0	—	24·3	9·9	—
20	—	—	—	18·1	20·3	14·7	22·2	16·5	31·5	—	—
21	—	—	10·3	13·6	—	13·7	27·5	28·8	27·0	—	—
22	—	—	—	—	—	26·1	25·6	9·3	18·9	—	—
23	—	5·2	9·7	13·2	10·5	16·6	—	9·3	13·7	—	—
24	—	5·2	9·5	13·0	19·8	26·5	10·0	—	13·3	—	—
25	—	—	—	15·9	—	24·8	18·9	19·9	14·5	—	—
26	—	9·9	9·0	7·8	—	25·1	14·3	19·3	12·0	8·2	—
27	—	—	—	7·7	—	15·1	9·8	18·4	11·2	—	—
28	—	6·8	10·1	7·3	—	6·6	—	8·7	7·3	—	—
29	—	4·5	—	—	—	6·3	—	9·5	6·6	—	—
30	—	—	—	—	9·8	7·3	—	7·3	7·8	—	—
31	—	—	—	—	7·6	6·9	—	—	6·9	—	—
32	—	—	—	—	—	—	—	—	—	—	—
33	—	—	—	—	—	8·9	—	4·6	—	—	—
34	—	—	—	—	—	7·8	—	—	—	—	—
35	—	—	—	—	9·8	—	—	—	—	—	—

(*h4l*)

	$l=4$	$l=3$	$l=2$	$l=1$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$
$h=0$	11·7	14·2	28·2	31·1	33·4	31·1	28·2	14·2	11·7
1	24·8	12·6	18·5	20·3	37·6	28·0	36·1	21·4	23·7
2	8·6	15·8	28·0	20·6	37·8	28·7	27·8	21·5	23·8
3	11·7	8·7	7·3	38·0	30·0	21·0	33·0	7·8	11·8
4	—	6·7	33·7	43·0	12·8	44·5	21·4	30·3	16·9
5	15·8	33·7	7·5	30·8	22·8	30·4	20·8	15·4	12·1
6	7·2	11·1	6·6	37·3	17·0	7·9	21·3	—	17·2
7	7·2	24·0	6·1	17·9	21·5	37·0	14·2	19·8	—
8	7·3	—	18·5	21·0	37·3	22·5	—	20·3	12·4
9	—	—	15·5	18·2	28·9	23·2	15·0	22·6	17·8
10	—	14·8	—	17·4	20·0	17·2	36·3	20·9	14·8
11	—	8·4	10·1	12·7	27·3	20·3	15·8	—	14·8
12	10·0	11·4	8·4	—	35·8	—	12·9	21·7	14·9
13	—	8·7	8·6	—	—	15·1	35·0	15·9	9·4
14	10·1	—	10·7	18·6	16·2	—	17·6	—	—
15	14·9	11·9	8·9	12·0	16·9	15·8	19·3	22·8	—
16	—	—	7·8	19·4	17·4	—	28·0	—	11·3

Table 4 (Cont'd.).

(h4l) contd.

	$l=\bar{4}$	$l=3$	$l=\bar{2}$	$l=\bar{1}$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$
$h=17$	—	—	14·5	12·4	23·0	19·4	8·7	—	11·1
18	—	—	17·9	—	—	15·8	—	—	8·9
19	—	12·2	—	15·8	13·6	15·8	8·1	—	7·1
20	—	—	8·1	15·8	9·9	19·8	18·1	12·5	6·8
21	—	—	10·4	11·7	7·0	12·9	8·0	9·7	7·9
22	—	7·6	10·4	—	—	11·7	—	—	6·2
23	—	7·5	—	—	—	11·7	—	—	11·1
24	6·1	11·1	7·8	—	9·8	—	17·7	10·1	14·4
25	7·2	7·0	—	—	—	—	26·0	—	—
26	—	8·6	7·3	—	9·3	—	6·7	—	7·3
27	—	6·2	6·9	—	9·0	—	—	—	—
28	5·4	—	—	—	10·1	9·6	20·0	—	—
29	4·4	—	—	8·4	11·5	8·8	9·6	—	—
30	—	—	—	8·6	6·6	9·3	10·3	—	—
31	—	—	—	7·6	—	—	7·8	—	—
32	—	—	—	—	—	9·3	—	—	—

(h5l)

	$l=\bar{4}$	$l=3$	$l=\bar{2}$	$l=\bar{1}$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$
$h=0$	7·6	—	—	10·3	—	10·3	—	—	7·6
1	12·7	9·8	8·4	—	12·6	—	25·1	16·8	7·6
2	9·3	9·8	13·3	17·2	5·0	—	14·7	16·8	12·1
3	8·5	9·8	—	12·2	20·6	—	18·2	—	10·2
4	—	—	—	8·8	17·0	15·1	12·5	10·8	10·2
5	8·6	—	11·3	8·8	13·6	15·3	15·0	15·8	10·2
6	8·6	—	29·8	29·9	24·2	35·6	18·5	—	14·9
7	8·6	—	27·5	10·8	—	25·6	26·2	15·9	7·8
8	—	11·9	15·3	25·6	7·7	25·8	34·6	9·0	—
9	—	11·9	7·7	9·8	10·0	26·1	—	14·4	9·4
10	—	9·0	—	10·0	22·0	26·5	18·1	8·0	14·8
11	—	12·0	13·2	10·0	6·6	16·0	—	8·0	9·3
12	—	8·0	8·6	—	6·7	—	—	8·0	—
13	—	11·2	13·5	11·5	6·7	—	—	—	—
14	—	8·0	8·7	11·7	13·6	12·9	—	—	—
15	—	—	8·7	11·7	11·9	24·4	—	—	—
16	—	—	—	—	—	10·0	—	—	—
17	—	—	8·1	—	14·0	—	—	—	—
18	—	—	—	—	8·6	14·1	—	9·5	—
19	—	—	—	10·0	7·0	—	9·0	11·9	8·3
20	—	—	—	11·7	7·0	—	—	9·0	—
21	—	—	—	—	6·9	—	8·6	—	6·5
22	—	—	7·7	—	—	—	—	11·5	4·8
23	—	—	—	—	8·2	—	8·0	7·6	4·2
24	—	—	7·0	—	9·7	17·2	—	7·0	—
25	—	—	—	—	13·0	—	—	7·5	—
26	—	—	—	—	6·0	—	—	5·5	—
27	—	—	—	—	5·7	6·9	—	3·6	—
28	—	—	—	—	4·5	6·0	—	—	—
29	—	—	—	—	—	6·9	6·0	—	—

Table 4 (Cont'd.).

(*h6l*)

	$l=4$	$l=3$	$l=2$	$l=1$	$l=0$	$l=1$	$l=2$	$l=3$	$l=4$
$h=0$	—	8·0	—	14·1	—	14·1	—	8·0	—
1	—	—	8·0	—	13·2	10·3	—	—	—
2	—	—	8·0	9·8	13·2	10·3	13·2	16·2	—
3	—	—	—	9·8	—	28·9	—	11·2	7·5
4	8·5	11·9	—	16·5	23·0	10·3	16·2	8·0	9·9
5	7·5	—	—	16·5	—	11·7	18·1	11·2	8·3
6	7·5	—	10·4	—	18·7	11·7	13·2	16·2	—
7	—	—	10·4	19·6	6·8	16·5	16·2	11·1	—
8	—	—	—	—	13·8	10·5	18·1	—	—
9	—	12·9	10·6	—	13·8	10·5	—	7·8	—
10	—	11·1	—	—	14·0	16·7	—	7·8	—
11	—	9·0	8·1	12·0	—	12·0	—	7·6	—
12	—	8·9	—	—	7·0	16·0	—	—	—
13	—	10·9	9·3	—	9·5	10·5	—	8·6	—
14	—	—	8·0	10·5	8·6	—	—	—	—
15	—	—	7·2	—	—	—	—	—	—
24	—	—	—	—	—	—	—	3·4	—

(*h7l*)

	$l=3$	$l=2$	$l=1$	$l=0$	$l=1$	$l=2$
$h=0$	—	—	—	—	—	—
1	—	—	—	—	—	—
2	—	—	10·5	—	12·9	—
3	—	—	—	—	—	—
4	—	—	—	—	—	—
5	—	—	—	—	—	9·0
6	—	—	—	7·0	—	11·0
7	—	—	—	—	—	9·0
8	—	—	—	—	—	—
9	—	—	9·8	8·6	—	—
10	8·1	—	—	7·0	—	—
11	—	8·7	—	8·5	—	—
12	—	10·7	—	—	—	—
13	—	8·4	—	—	—	—
14	—	—	—	9·2	—	—

DISCUSSION

The iresin molecule (IV) was found to have the angular methyl attached to C-10. Rings A and B are fused *trans*. The fact that the OH group on C-3, the methylene group on C-4 and the 5–6 bond are all *cis* has been confirmed. Ring A is in chair form. Rings B and C are very roughly in the same plane, except for atom C-5. However, the H on C-9 and the methyl C-15 are *trans* (Fig. 5), in agreement with the chemical results of Djerassi *et al.*[5] The shape of the molecule and its packing in the crystal can be seen in Figs. 5 and 6.

The standard deviations of the atomic position parameters, calculated from the residuals in the least-squares refinement, were essentially isotropic. Their values (Fig. 7) led to estimated standard deviations of 0·035, 0·050, 0·042 Å in the Br–C, C–C and C–O bond lengths, respectively. As an independent estimate, the mean

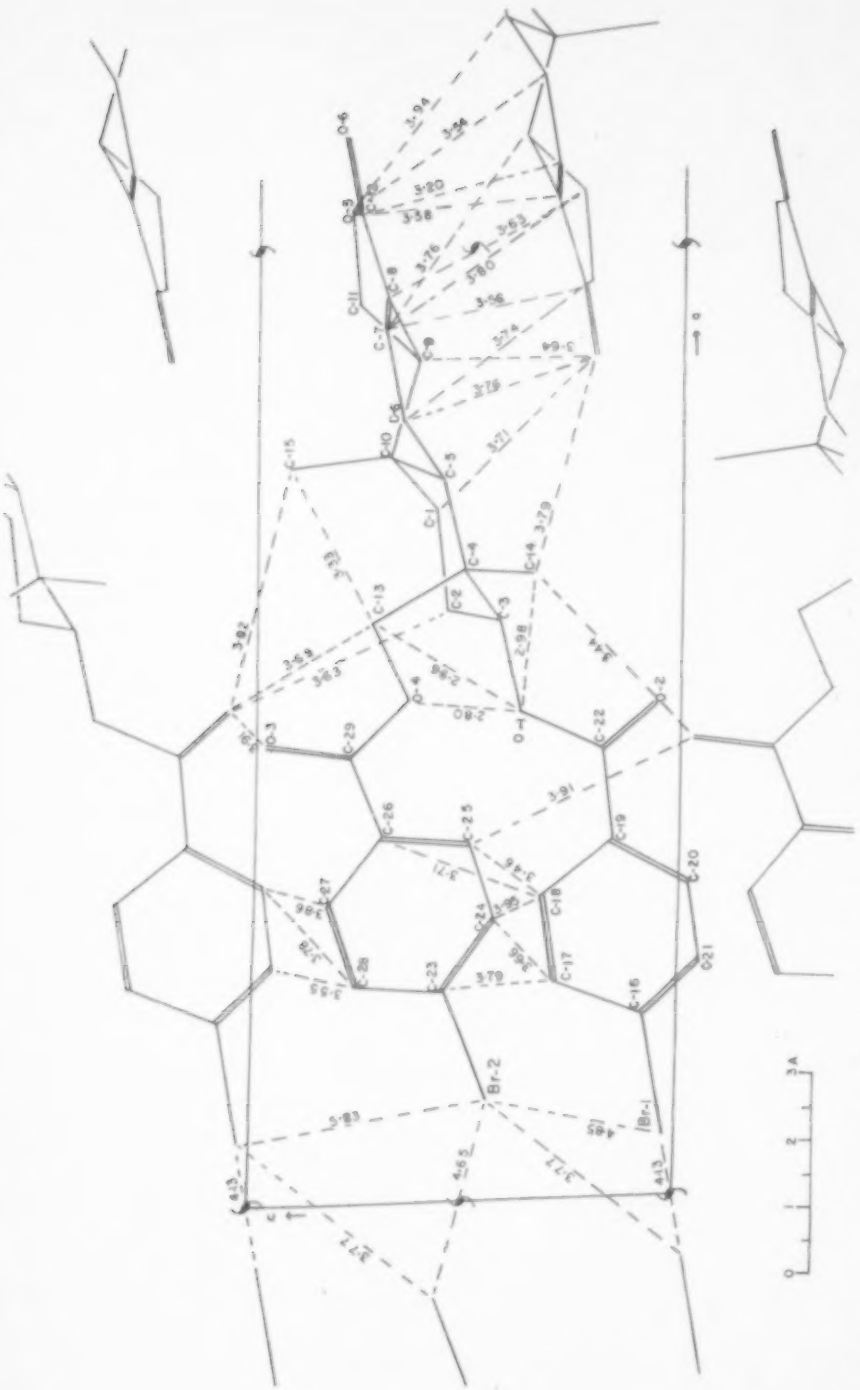


FIG. 5. Diagram showing projection of the molecule along the *b* axis, its packing and intermolecular distances.

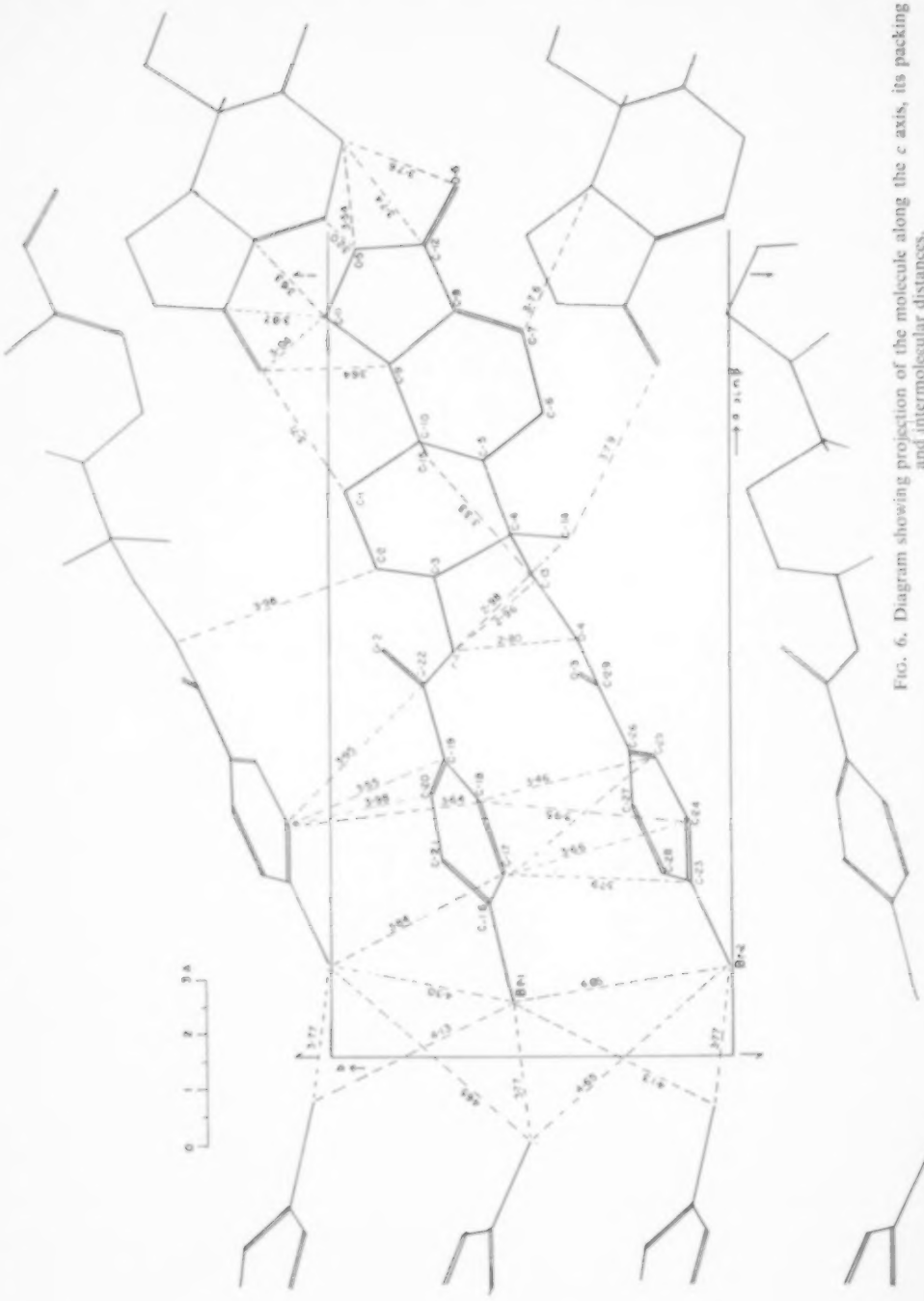
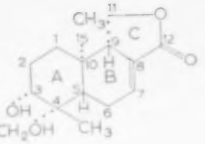


FIG. 6. Diagram showing projection of the molecule along the c axis, its packing and intermolecular distances.

VOL.
4
195

distance of 1·395 Å for the twelve C–C bonds in the two benzene rings gave a standard deviation of 0·068 Å, quite reasonably a bit higher than the least-squares value of 0·050 Å obtained by neglect of off-diagonal terms in solving the normal equations.



IV

Standard deviations in bond angles (Fig. 7) were about 4°. The fact that bonds C-22 · · · O-2, C-29 · · · O-3, C-29 · · · O-4, C-12 · · · O-6 and C-12 · · · O-5 are significantly shorter than a single C · · · C bond of 1·54 Å, establishes that O-2, O-3, O-4, O-5 and O-6 are oxygen atoms. Also, their higher electron density (Fig. 4) and yet sensible temperature factors (Fig. 7) further confirms this point. The shortness of the bond C-8 · · · C-7, as well as the general planarity of ring B establishes the position of the double bond in ring B.

The benzene ring attached to Br-1 and the corresponding carboxyl group and atom C-3 all lie in the same plane. The maximum distance of any one atom from this plane is 0·2 Å. In contrast, the benzene ring attached to Br-2 does not lie in the same plane as its corresponding carboxyl group. The maximum distance of any one atom from the best plane representing the benzene ring was 0·10 Å. The carboxyl group, methylene group and atom C-4 are roughly co-planar to within 0·5 Å. The angle between the normal to the benzene ring attached to Br-2 and the plane through the corresponding carboxyl group is 59°. The five-membered ring and atom O-6 was planar to within 0·09 Å, except for atom C-9, which is 0·44 Å from this mean plane. Exactly the same degree of non-planarity is found in similar five-membered rings.[9] As a general rule, one of the two carbon atoms furthest away from the oxygen is displaced by about 0·4 Å from the plane of the other four atoms. Atoms C-6, C-7 and C-10 lie on the same side of and between 0·25 to 0·35 Å away from the five membered ring plane.

Inter-molecular distances less than 4·0 Å, shown in Figs. 5 and 6, indicate no contacts significantly less than Van der Waals distances. All close C · · · C contacts are just greater than 3·4 Å, the recognized Van der Waals C · · · C distance. The close C · · · O contact of 3·20 Å between molecules related by a twofold screw is also just greater than the C · · · O Van der Waals contact distance of 3·1 Å. Within the molecule the methylene group C-13 and the methyl C-15 approach to 3·33 Å, and the oxygen O-1 approaches the methylene C-13 and methyl C-14 to 2·96 and 2·98 Å, respectively. Similarly, the two ether oxygens O-1 and O-4 approach to exactly the limit set by the sum of their radii, presumably because they are unhindered by hydrogen atoms. The angle between the normals of the two benzene rings is 50½°, which compares very favourably with about 52° in naphthalene and anthracene. Had it not been so difficult to obtain good single crystals, we would marvel at how well Nature is able to pack such an awkwardly shaped molecule.

[9] F. Jellinek, *Acta Cryst.* **10**, 277 (1957); S. Furberg, *Ibid.* **3**, 325 (1950); and L. A. Beevers and W. Cochran, *Proc. Roy. Soc.* A **190**, 257 (1947).

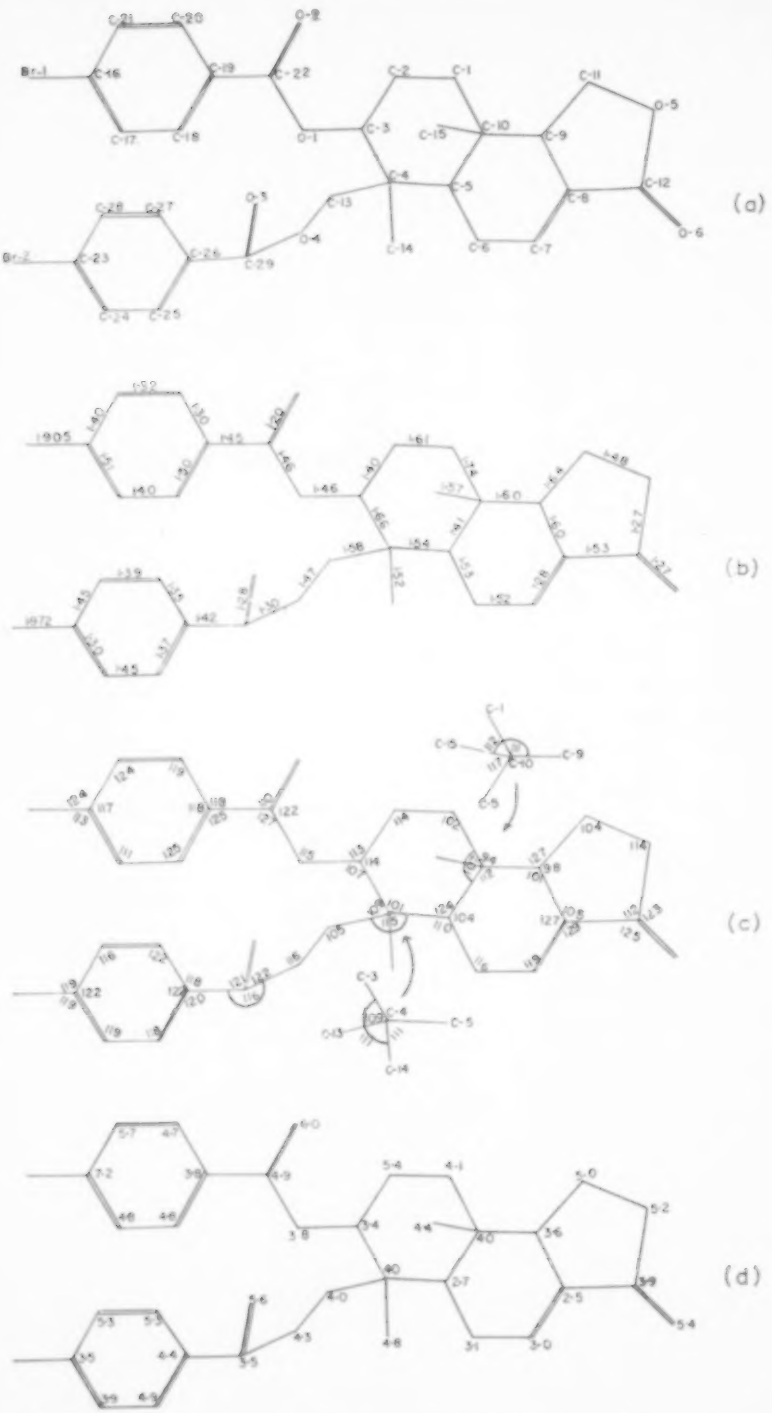


FIG. 7. Diagram (a) gives the atomic names. Diagram (b) shows bond length. Diagram (c) shows bond angles. Diagram (d) shows final isotropic temperature factors.

ANISOTROPIC THERMAL MOTION OF THE Br ATOMS

The determination of amplitudes of vibration by least-squares methods for individual atoms[10,11] is adopted here as being more suitable than the analysis of the motion of a rigid molecule[12] and to the analysis of electron density gradients in difference projections[13] or three-dimensional difference maps.[14] For an isotropic atom the atomic amplitude of scattering is reduced by $\exp(-\mathbf{B}\sin^2\theta/\lambda^2)$ where $\mathbf{B}$ is related to the mean square amplitude of vibration by $\mathbf{B} = 8\pi^2\mu^2$, and is usually expressed in units of Å^2. When the motion is anisotropic, the usual form is $\exp[-(\beta_1h^2 + \beta_2k^2 + \beta_3l^2 + \beta_4hk + \beta_5kl + \beta_6hl]$ where the β's are determined from the experimental data by the least-squares treatment. If we substitute $A = 4\beta_1/a^{*2}$, $B = 4\beta_2/b^{*2}$, $C = 4\beta_3/c^{*2}$, $D = 4\beta_4a^*b^*$, $E = 4\beta_5/b^*c^*$ and $F = 4\beta_6/c^*a^*$, then in an orthogonal system of axes, where 2ϕ, 2ψ, 2ω is a point in reciprocal space and $\phi^2 + \psi^2 + \omega^2 = 1$, we can express $\mathbf{B}$ as

$$\mathbf{B} = A\phi^2 + B\psi^2 + C\omega^2 + D\phi\psi + E\psi\omega + F\omega\phi \tag{1}$$

The values of ϕ, ψ and ω which define the directions of the principal axes of the ellipsoid of vibration are given by the simultaneous solutions of

$$\left.\begin{aligned}(2A - \lambda)\phi + D\psi + F\omega &= 0\\ D\phi + (2B - \lambda)\psi + E\omega &= 0\\ F\phi + E\psi + (2C - \lambda)\omega &= 0\end{aligned}\right\} \tag{2}$$

when λ is a root of

$$\lambda^3 + p\lambda^2 + q\lambda + r = 0$$

where

$$\begin{aligned}p &= -2(A + B + C)\\ q &= 4(AB + BC + CA) - (D^2 + E^2 + F^2)\\ r &= -2[4ABC - (AE^2 + BF^2 + CD^2) + DEF]\end{aligned} \tag{3}$$

Then the three solutions of the cubic equation correspond to the three principal directions of the ellipsoid of vibration.*

The experimental data are the β's listed in Table 5 corresponding to the bromine

TABLE 5. ANISOTROPIC THERMAL PARAMETERS FOR BROMINE ATOMS

	Br-1	Br-2		Br-1	Br-2
β_1	0·0012	0·0012	A	3·9	3·9
β_2	0·0522	0·0467	B	11·5	10·3
β_3	0·0636	0·0553	C	10·4	9·0
β_4	−0·0002	−0·0036	D	−0·2	−3·0
β_5	−0·0108	−0·0193	E	−2·0	−3·6
β_6	−0·0055	−0·0050	F	−4·0	−3·6

* In the monoclinic system (b unique), A, B and D remain as defined above, but
$C = (\csc\beta^*)[4\beta_3/c^{*2} - 4\beta_6(\cos\beta^*)/c^*a^* + 4\beta_1(\cos^2\beta^*)/a^{*2}]$,
$E = (\csc\beta^*)[4\beta_5/b^*c^* - 4\beta_4(\cos\beta^*)/a^*b^*]$, and
$F = (\csc\beta^*)[4\beta_6/c^*a^* - 8\beta_1(\cos\beta^*)/a^{*2}]$.
when a, b and an axis perpendicular to a and b are chosen as orthogonal axes.

[10] J. S. Rollett and D. R. Davies, *Acta Cryst.* **8**, 125 (1955).
[11] J. Waser, *Acta Cryst.* **8**, 731 (1955).
[12] D. W. J. Cruickshank, *Acta Cryst.* **9**, 754 (1956).
[13] W. Cochran, *Acta Cryst.* **4**, 81 (1951); *Ibid.* **4**, 408 (1951).
[14] Y. C. Leung, R. E. Marsh and V. Schomaker, *Acta Cryst.* **10**, 650 (1957).

co-ordinates given in Table 3. These values were converted to $A \cdots F$ with the use of the unit cell parameters. The procedure, probably to be found useful in other similar cases, is as follows. For a given Br, substitute $A \cdots F$ into (3), solve for the roots λ_1, λ_2 and λ_3 by convenient graphical procedures, then substitute each root into (2) in order to find the proportions $\phi : \psi : \omega$, and then divide these final results by $\sqrt{\phi^2 + \psi^2 + \omega^2}$ to obtain the actual direction cosines (Table 6) which can be inserted into equation (1) to find the magnitude of the temperature factor in the direction of each principal axis (Table 6).

Table 6. Direction and magnitude of principal axes of ellipsoid of vibration

	λ	ϕ	ψ	ω	B	
Br-1	6·7	0·963	0·042	0·265	3·3	*L*
	20·7	0·230	−0·597	−0·769	10·3	*M*
	24·4	0·128	0·814	−0·571	12·1	*N*
Br-2	5·6	0·910	0·263	0·328	2·8	*L*
	17·7	0·426	−0·498	−0·758	8·9	*N*
	23·1	0·034	−0·839	0·547	11·6	*M*

If we label these principal axes (Table 6) by *L*, *M*, *N* and if we name the direction of the Br $\cdots$ C bond as *P*, the normal to the benzene ring as *Q*, and an axis in the plane of each benzene ring and perpendicular to *P* and *Q* as *R*, then the angles which *L*, *M* and *N* make with *P*, *Q* and *R* are shown in Table 7.

Table 7. The angles between the principal axes of vibration with given directions in the corresponding benzene ring

Angle	Br_1	Br_2
$\angle L, P$	14°	8°
$\angle M, Q$	27°	20°
$\angle N, R$	30°	20°

Thus we see that a fairly "normal" amplitude of vibration exists in a direction parallel to the Br $\cdots$ C bonds, while the motion perpendicular to this bond is extraordinarily large. There is apparently no correlation between the plane of the benzene rings and the direction of the major axes. It does seem surprising that there is no conclusive evidence of anisotropic thermal motion in the atoms of the benzene ring in D2, as one would expect from the apparent anisotropic motion of the Br atoms, or from possible randomness in the position of the benzoate groups by about 0·35 Å perpendicular to the Br $\cdots$ C bond. From this analysis it would seem that the short Br $\cdots$ Br contact of 3·77 Å, just over the Van der Waals contact distance, is a very important feature of the molecular packing.

The standard deviation of **B** in any given direction is 0·4 Å² for the bromine atoms and 0·6 Å² for the isotropic atoms.

CALCULATIONS

All calculations were carried out on the Remington Rand UNIVAC 1103 high-speed digital computer. Phases used to compute Fourier summations were written onto magnetic tape during a least-squares calculation. These were then read back into the computer and sorted in such a way as to be suitable for our Fourier program. The *a*, *b* and *c* axes were divided into 160, 40 and 20 parts so that the intervals in these directions measured 0·18, 0·19 and 0·32 Å, respectively. The time required to punch the electron density at all the 64,000 points in the asymmetric unit was 2½ hr. One least-squares refinement cycle, when all atoms were included, and the bromine atoms were given six thermal parameters each, took 64 min. 1430 reflections were included in all Fourier summations and least-squares calculations. The Thomas–Fermi[15] scattering curve was used for bromine but McWeeny[16] curves were used for oxygen and carbon. A total of 39 hr of computing was used in this study.

Acknowledgements—We wish to express our thanks to Professor C. Djerassi who suggested this problem to us and who also supplied the sample of iresin. We are also indebted to Dr. P. Tomboulion who prepared the heavy atom derivative, and to the University of Minnesota for contributing the computing time. This research was also aided by a grant from the Upjohn Company.

[15] *Internationale Tabellen* p. 572. Zweiter Band, Berlin (1935).
[16] F. McWeeny, *Acta Cryst.* **4**, 513 (1951).

Tetrahedron, 1958, Vol. 4, pp. 294–301. Pergamon Press Ltd., London

A STEREOSPECIFIC SYNTHESIS OF (±)-FERRUGINOL*

P. NARASIMHA RAO†
Division of Organic Chemistry, National Chemical Laboratory, Poona 8, India
and
K. RAMAN
Department of Organic Chemistry, Indian Institute of Science, Bangalore, India

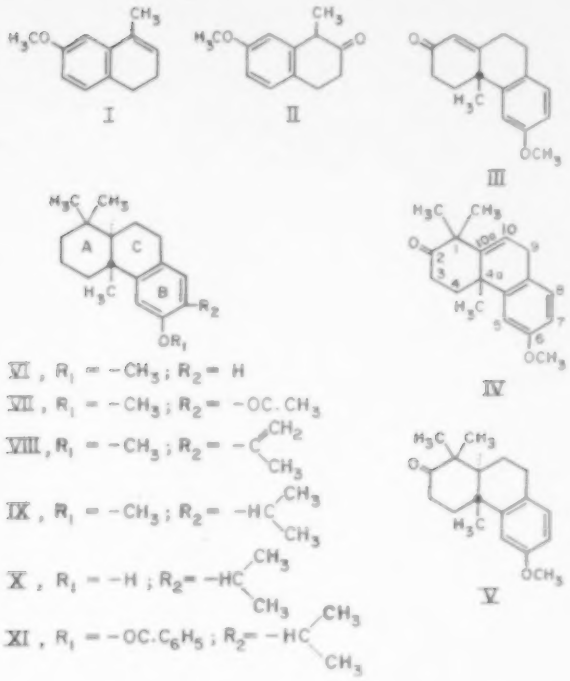
(*Received* 20 *May* 1958)

Abstract—A stereospecific synthesis of (±)-ferruginol following the Robinson "ring extension" method has been described. The infra-red spectra of the benzoates of the synthetic and natural ferruginol are found to be identical.

THE phenolic diterpene, ferruginol, comprises the major part of the resin of the Miro tree (*Podocarpus ferruginea*) endemic to New Zealand and was first isolated by Brandt and Newbauer.[1] The structure of ferruginol (X), was established with certainty[1,2] and its partial syntheses were achieved from podocarpic acid and dehydroabietic acid.[3] From a study of thermodynamic dissociation constant data, Barton and Schmeidler[4] had concluded that the A/C ring junction in the diterpenoids is *trans*, and this was confirmed by the first total synthesis of (±)-ferruginol by King *et al.*[5] However, the synthetic route followed by King *et al.* is not stereospecific, because the important intermediate 1:1-dimethyl-4*a*-methyl-6-methoxy-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene (VI) was obtained as a mixture of stereoisomers, from which the natural *trans* isomer was obtained in low yield by a laborious process. It is therefore desirable to develop a stereospecific synthetic route whereby the *trans* isomer could be obtained predominantly. We have now achieved this objective and synthesised 1:1-dimethyl-4*a*-methyl-6-methoxy-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene (VI), following the Robinson "ring extension" method[6] and transformed compound (VI) to (±)-ferruginol.

1-Methyl-7-methoxy-3:4-dihydronaphthalene[7] (I) was oxidised in acetic acid solution with red lead oxide[8] and the crude diacetate rearranged in dilute alcoholic sulphuric acid to 1-methyl-7-methoxytetralone-2 (II) in 70 per cent yield. Condensation of the β-tetralone (II) with 4-diethylaminobutanone-2-methiodide,[6] or with methyl vinyl ketone afforded, 6-methoxy-2-keto-4*a*-methyl-2:3:4:4*a*:9:10:hexahydrophenanthrene (III), as a very viscous oil, which ultimately crystallised with difficulty to give rhomboid prisms, m.p. 72°. Of the two methods, the Robinson–Mannich base procedure gave superior yields of the ketone (III) (60 per cent) to the methyl vinyl ketone procedure (45 per cent). The ketone (III) gave a deep red

* For preliminary communication, see *Experientia* **12**, 472 (1956).
† To whom all communications about this paper should be addressed.
[1] C. W. Brandt and L. G. Newbauer, *J. Chem. Soc.* 1031 (1939).
[2] W. P. Campbell and D. Todd *J. Amer. Chem. Soc.* **62**, 1287 (1940).
[3] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.* **64**, 928 (1942).
[4] D. H. R. Barton and G. A. Schmeidler, *J. Chem. Soc.* 1197 (1948).
[5] F. E. King, T. J. King and J. G. Toplis, *Chem. & Ind.* 108, (1954); *J. Chem. Soc.* 573 (1957).
[6] E. C. du Few, F. J. McQwuillin and R. Robinson, *J. Chem. Soc.* 53 (1937).
[7] P. C. Mitter and S. De, *J. Indian Chem. Soc.* **16**, 35 (1939).
[8] W. F. Newhall, S. A. Harris, F. W. Holly, E. L. Johnston, J. W. Richter, E. Walton, A. N. Wilson and K. Folkers, *J. Amer. Chem. Soc.* 77, 5646 (1955).



2:4-dinitrophenylhydrazone, which exists in two different forms, depending upon the solvent from which it was crystallised. When crystallised from acetic acid, it was obtained as rectangular plates, m.p. 242° (dec.), whereas if crystallised from ethyl acetate it was obtained as prisms, m.p. 200°. A *gem*-dimethyl group was then introduced in one step[9] by allowing the ketone (III) to react with methyl iodide in the presence of potassium *tert.*-butoxide in *tert.*-butyl alcohol solution, to give 1:1-dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9-hexahydrophenanthrene (IV) as a viscous oil. A clear separation of the dimethylated product (IV) from the unreacted ketone (III) could not be achieved by fractional distillation in high vacuum as evidenced by the infra-red spectra data. However, the pure dimethylated product (IV) could be separated from the unreacted product through its crystalline 2:4-dinitro-phenylhydrazone by fractional crystallisation from ethyl acetate, and then regenerating the ketone according to the method of Demaecker and Martin,[10] in 55 per cent yield. All efforts to obtain the ketone (IV) in a crystalline form were unsuccessful. The compound (IV) on hydrogenation with 10% palladium–charcoal in acetic acid afforded *trans*-1:1-dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene (V). The *trans* configuration is assigned to this compound by a consideration of the following facts:

(1) It is well known that hydrogenation of Δ^5-steriods invariably leads to the *trans* configuration at the A/B ring junction and compound (IV) is similar in structure to a Δ^5-st:roid.

[9] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Amer. Chem. Soc.* **76,** 2852 (1954); *J. Chem. Soc.* 1131 (1957).
[10] J. Demaecker and R. H. Martin, *Nature, Lond.* **173,** 266 (1954).

(2) During the hydrogenation of the compound (IV) the absorption of the catalyst on the α-face of the C-10:10*a* is not sterically hindered, whereas the β-face is highly hindered by the C-1 β-axial methyl and C-4*a* angular methyl groups. Consequently the A/C ring junction in compound (V) will be *trans*.

(3) Further, recent work[11] on hydrogenation of compounds having similar structure (IV) definitely established that the hydrogenated product will have the *trans* configuration.

The keto group in compound (V) was reduced by Clemmensen's method to give *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene (VI) in 75 per cent yield.

An *iso*propyl group was then introduced at the 7- position of the *trans*-octahydrophenanthrene (VI) by a procedure similar to that described by King *et al*. Compound (VI) was subjected to reaction with acetyl chloride in nitrobenzene in presence of aluminium chloride to yield *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-7-acetyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene (VII) in excellent yield. This compound gave the semicarbazone of m.p. 222–223°, already shown to be *trans*,[5] in 80 per cent yield as the only isomer. This further supports the *trans* structure assigned to compound (VI). Compound (VII) was subjected to Grignard reaction with methylmagnesium iodide to give the carbinol, which upon dehydration with acetic anhydride gave *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-7-*iso*propenyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene (VIII). This was smoothly hydrogenated in alcoholic solution over platinum oxide catalyst to yield *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-7-*iso*propyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene, (±)-ferruginy methyl ether (IX). This was then demethylated by heating with pyridine hydrochloride at 160° in an atmosphere of nitrogen to give (±)-ferruginol as a resin, which gave a crystalline benzoate, m.p. 132°, and was in good agreement with that described by King *et al*.[5] Further, confirmation of the structure of the synthetic product was obtained by the identity of the infra-red spectra of the synthetic and natural ferruginyl benzoates.

EXPERIMENTAL*

7-*Methoxytetralone*-1. This compound was prepared according to the modified procedure described by Krishna Rao and Sukh Dev.[12]

1-*Methyl*-7-*methoxy*-3:4-*dihydronaphthalene* (I). 6-Methoxytetralone-1 was subjected to Grignard reaction with methylmagnesium iodide according to the procedure worked out by Mitter and De.[7]

1-*Methyl*-7-*methoxytetralone*-2 (II). A mixture of 36·7 g of 1-methyl-7-methoxy-3:4-dihydronaphthalene, 0·4 g of sodium acetate, 250 ml of glacial acetic acid and 40·5 ml of acetic anhydride was heated to 55°. The addition of 143 g of red lead oxide was performed with stirring at such a rate that the temperature of the reaction mixture was maintained at 57–59°. After the addition was complete, about 150 ml of acetic acid was removed under reduced pressure, and the residue was diluted with water and extracted with ether. The ether extract was washed with water, 10%

* All melting points and boiling points are uncorrected.

[11] G. Stork and W. J. Schwlenberg, *J. Amer. Chem. Soc.* **78**, 250 (1956); J. D. Cocker and T. G. Halsall, *Chem. & Ind.* 1275 (1956); J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips *J. Chem. Soc.* 735 (1957); H. J. Ringold and G. Rosenkranz, *J. Org. Chem.* **22**, 602 (1957); F. Sondheimer and D. Elad, *J. Amer. Chem. Soc.* **79**, 5542 (1957).

[12] G. S. Krishna Rao and Sukh Dev, *J. Indian Chem. Soc.* **34**, 255 (1957).

sodium bicarbonate solution and then with water and dried over anhydrous sodium sulphate. The solvent was removed and 51 g of the crude residue of the diacetate was subjected to hydrolysis without further purification.

A mixture of 51 g of the above diacetate in 80 ml of ethanol, 115 ml of water and 21·5 ml of concentrated sulphuric acid was heated under reflux for 2 hr on a water bath. The mixture was then diluted with large volume of water and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed and the residue was distilled under vacuum using a 6 in. fractionating column. 1-Methyl-7-methoxytetralone-2 (II), distilled at 125–126°/0·8 mm, n_D^{25} 1·5538, as a colourless liquid; yield 19·1 g (70 per cent) (Found: C, 76·1; H, 7·4. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4 per cent).

Semicarbazone of 1-*methyl*-7-*methoxytetralone*-2. To a mixture of 1·5 g of semicarbazide hydrochloride and 1·5 g of fused sodium acetate in 10 ml of aqueous alcohol, 0·8 g of the β-tetralone was added, and within a few minutes the semicarbazone separated out in the cold. This was filtered off and crystallised from alcohol to give colourless prisms, m.p. 191–192° (Found: N, 17·2. Calc. for $C_{13}H_{17}O_2N_3$: N, 17·0 per cent).

2-*Keto*-6-*methoxy*-4a-*methyl*-2:3:4:4a:9:10-*hexahydrophenanthrene* (III). Using a *diethylaminobutaneone* 2-*methiodide*. To 13·17 g (15·5 ml) of diethylaminobutaneone-2 cooled in ice, 13·12 g (5·8 ml) of methyl iodide was added with constant swirling and in small portions, and swirling continued for ½ hr after addition of methyl iodide, when the methiodide was obtained in a crystalline form. A solution of 17·5 g of β-tetralone in 85 ml of thiophene-free dry benzene was added to the methiodide in an atmosphere of dry nitrogen. A solution of 5·7 g of potassium in 85 ml of absolute alcohol was added with swirling to the mixture cooled in ice. After ½ hr the methiodide has disappeared and a fine precipitate of potassium iodide separated. The contents were left in ice for 1 hr, and then the mixture was gently boiled for ½ hr. An excess of 2 N sulphuric acid was added, the reaction product was diluted with water and the benzene layer was separated. The aqueous layer was extracted twice with ether and the combined ether–benzene extracts were washed with water and dried over anhydrous sodium sulphate. The solvents were removed and the residue on distillation gave 2-keto-6-methoxy-4*a*-methyl-2:3:4:4*a*:9:10-hexahydrophenanthrene, b.p. 115–120° (bath temperature)/0·004 mm, as a very viscous liquid; yield 19 g. This was dissolved in 20 ml of ether and kept at 0°. After 1 week the product slowly crystallised and it was kept at 0° for 24 hr and filtered off (13·5 g, 60 per cent), m.p. 69°. The analytical sample was crystallised twice from light petroleum (boiling range 40–60°), m.p. 73° (Found: C, 79·3; H, 7·5. Calc. for $C_{16}H_{28}O_2$: C, 79·1; H, 7·6 per cent).

2:4-*Dinitrophenylhydrazone of* (III). A sample of 0·5 g of the ketone was treated with an alcoholic solution of 2:4-dinitrophenylhydrazine sulphate, and the crystalline 2:4-dinitrophenylhydrazone thus formed was filtered off. After two crystallisations from acetic acid, the m.p. 241–242° was constant; shining deep red rectangular plates were obtained. (Found: C, 62·9; H, 5·5; N, 12·8. Calc. for $C_{13}H_{17}O_2N_3$: C, 62·6; H, 5·3; N, 13·3 per cent).

The crude 2:4-dinitrophenylhydrazone was twice crystallised from ethyl acetate to the constant m.p. 200°; shining deep red prisms were obtained. (Found: C, 62·6; H, 5·4. Calc. for $C_{13}H_{17}O_2N_3$: C, 62·6; H, 5·3 per cent).

2-Keto-6-methoxy-4a-methyl-2:3:4:4a:9:10-hexahydrophenanthrene (III) *using methyl vinyl ketone.* A solution of 9·35 g of 1-methyl-7-methoxytetralone-2 in 40 ml of alcohol was treated under nitrogen with a solution of 6·3 ml of 40% benzyltrimethylammonium hydroxide solution in 40 ml of alcohol, and the mixture was cooled to 0°. A solution of 4 ml of 85% methyl vinyl ketone in 40 ml of alcohol was added with stirring during ½ hr. The stirring was continued for 1 hr at 0°, and the solution was then refluxed for ½ hr. The reaction mixture was cooled and acidified with 2 N sulphuric acid, and diluted with water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution and finally with water until neutral. After drying over anhydrous sodium sulphate, the solvent was removed and the residue was distilled as above. The product was dissolved in 5 ml of ether and kept at 0°, when 5·4 g (45 per cent) of 2-keto-6-methoxy-4*a*-methyl-2:3:4:4*a*:9:10-hexahydrophenanthrene crystallised as light-yellow prisms, m.p. 70°. The mixed melting point with the product obtained by the previous method showed no depression.

1:1-*Dimethyl-2-keto-6-methoxy-4a-methyl-1:2:3:4:4a:9-hexahydrophenanthrene* (IV). To a solution of 5·9 g of potassium in 200 ml of *tert.*-butyl alcohol was added 12 g of 2-keto-6-methoxy-4*a*-methyl-2:3:4:4*a*:9:10-hexahydrophenanthrene, and the mixture was mechanically stirred until the solid dissolved. The solution was cooled in ice and 42·6 g of methyl iodide was added. The mixture was stirred at room temperature for 2 hr, when potassium iodide separated, and after refluxing for ½ hr most of the solvent was removed under reduced pressure. The residue was treated with water and the product was extracted with ether and after removal of the solvent, 13 g of the crude product was purified through its 2:4-dinitrophenylhydrazone as described below:

Preparation of the pure 2:4-*dinitrophenylhydrazone of* (IV). A mixture of 9·5 g of 2:4-dinitrophenylhydrazine, 500 ml of alcohol and 20 ml of concentrated hydrochloric acid was heated under reflux on a water bath. When all the solid had dissolved, the solution was filtered and cooled to room temperature. To the solution 13 g of the crude ketone in 200 ml of alcohol was added, and the mixture was stirred. The 2:4-dinitrophenylhydrazone was filtered off and washed with a little cold alcohol, and, after drying, the product weighed 19 g and was crystallised from ethyl acetate. The first crop of 13 g melted at 212°, and the subsequent fractions consisted of a mixture of 2:4-dinitrophenylhydrazones of the original ketone and the methylated product, and could not be purified. The analytical sample was crystallised once more from ethyl acetate and the m.p. 213° was constant; orange red prisms were obtained. (Found: C, 64·0; H, 5·9. Calc. for $C_{24}H_{26}O_5N_4$: C, 64·0; H, 5·8 per cent).

The 2:4-dinitrophenylhydrazone of 1:1-dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9-hexahydrophenanthrene crystallised from glacial acetic acid with a molecule of solvent, m.p. 238–240° (dec.) (Found: N, 11·1. Calc for $C_{24}H_{26}O_5N_4$: CH_3COOH: N, 11·0 per cent).

Regeneration of the ketone (V) *from its* 2:4-*dinitrophenyl-drazone.* A solution of 12 g of the 2:4-dinitrophenylhydrazone in 1500 ml of acetone and 50 ml of concentrated hydrochloric acid was refluxed for 1 hr under nitrogen on a steam-bath. It was cooled and a solution of 60 g of stannous chloride in 250 ml of concentrated hydrochloric acid and 330 ml of water was added and refluxed for 2 hr. The acetone was removed under reduced pressure, and the residue was diluted with 1 l. of water and extracted with benzene, and the extract was washed with N hydrochloric acid until

the washings were colourless and then with water until neutral. The benzene was removed and the residue was slowly distilled from an air-bath kept at 120–125°/0·004 mm. 1:1-Dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9-hexahydrophenanthrene (IV) was obtained as a viscous oil; yield 7·45 g (55 per cent) (Found: C, 79·9; H, 8·2. Calc. for $C_{18}H_{22}O_2$: C, 79·9; H, 8·2 per cent).

All attempts to crystallise the oil were unsuccessful.

trans-1:1-*Dimethyl*-2-*keto*-5-*methoxy*-4a-*methyl*-1:2:3:4:4a:9:10:10a-*octahydrophenanthrene* (V). A solution of 7·4 g of 1:1-dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9-hexahydrophenanthrene in 100 ml of glacial acetic acid was hydrogenated in the presence of 0·5 g of 10% palladium on charcoal at room temperature. After the calculated amount of hydrogen had been absorbed, the solution was filtered and the acetic acid was removed under reduced pressure. The residue was dissolved in benzene and washed with water, sodium bicarbonate solution and again with water. The solvent was removed and the product was distilled in vacuum. *trans*-1:1-Dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene distilled at 180–184°/0·8 mm, as a colourless viscous oil: yield 7·2 g (Found: C, 79·8: H, 8·9. Calc. for $C_{18}H_{24}O_2$: C, 79·4; H, 8·9 per cent).

2:4-*Dinitrophenylhydrazone of* (V). The 2:4-dinitrophenylhydrazone of 1:1-dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene was prepared in the usual manner and crystallised from ethyl acetate. The analytical sample after two crystallisations from ethyl acetate melted at 198–199° (Found: N, 12·3. Calc. for $C_{24}H_{28}O_5N_4$: N, 12·3 per cent).

trans-1:1-*Dimethyl*-4a-*methyl*-6-*methoxy*-1:2:3:4:4a:9:10:10a-*octahydrophenanthrene* (VI). Seven grams of *trans*-1:1-dimethyl-2-keto-6-methoxy-4*a*-methyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene and 60 ml of diluted hydrochloric acid (1:1) were added to amalgamated zinc, prepared by treating 50 g of reagent-quality zinc for 15 min with a solution of 5 g of mercuric chloride, 4 ml of concentrated hydrochloric acid and 60 ml of water, and heated under reflux for 40 hr in an oil-bath at 135°. During refluxing at intervals of 6 hr concentrated hydrochloric acid (5 ml) was added. The contents were decanted from the zinc, and the organic matter was dissolved in ether, and the ether solution was washed with water, 5% sodium hydroxide solution (to remove any demethylated product) and finally with water until neutral. After removal of the solvent, the residue was distilled over sodium. *trans*-1:1-Dimethyl-4*a*-methyl-6-methoxy-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene distilled at 145–147°/0·8 mm, as a colourless mobile oil; yield 5 g (75 per cent), n_D^{26} 1·5465. (lit.[6] b.p. 122–124°/0·2 mm, n_D^{20} 1·5478) (Found: C, 83·8; H, 10·2. Calc. for $C_{18}H_{26}O$: C, 83·7; H, 10·1 per cent).

trans-1:1-*Dimethyl*-4a-*methyl*-6-*methoxy*-7-*acetyl*-1:2:3:4:4a:9:10:10a-*octahydrophenanthrene* (VII). To a solution of 5 g of *trans*-1.1-dimethyl-4*a*-methyl-6-methoxy-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene and 3 ml of acetyl chloride in 50 ml of nitrobenzene at 5–8°, 6 g of finely powdered anhydrous aluminium chloride was added in small portions and the contents were left at 10° for 75 hr with occasional shaking. The reaction mixture was decomposed with 50 ml of concentrated hydrochloric acid and the nitrobenzene was removed by steam distillation. The residue was extracted with ether, and the extract was washed with water till neutral and dried over sodium sulphate. The residue after removal of the ether was distilled in vacuum and *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-7-acetyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene

(5 g), b.p. 185–190°/0·2 mm, was obtained as a viscous oil (Found: C, 80·1; H, 9·2. Calc. for $C_{20}H_{28}O_2$: C, 80·0; H, 9·4 per cent).

Semicarbazone of (VII). To a solution of 1 g of semicarbazide hydrochloride and 1 g of fused sodium acetate in 6 ml of alcohol, 0·3 g of the ketone (VII) was added and the mixture was heated on a water bath for ½ hr and kept at 10° for 2 days. The precipitated semicarbazone was filtered off (0·3 g, 80 per cent yield), m.p. 219–220°. The analytical sample was crystallised from methanol, m.p. 222–223° (King *et al.*[5] give 222–223°) (Found: C, 70·8; H, 8·4. Calc. for $C_{21}H_{31}O_2N_3$: C, 70·6; H, 8·7 per cent).

trans-1:1-*Dimethyl*-4a-*methyl*-6-*methoxy*-7-iso*propenyl*-1:2:3:4:4a:9:10:10a-*octahydrophenanthrene* (VII). A solution of 3·4 g of *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-7-acetyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene in 80 ml of dry ether was added with stirring to a solution of methylmagnesium iodide prepared from 1·8 g of magnesium and 4 ml of methyl iodide in 100 ml of dry ether. The contents were stirred at room temperature for 4 hr and then gently refluxed for ½ hr. The reaction mixture was then decomposed with saturated ammonium chloride solution and the ether layer was separated. The aqueous layer was extracted twice with ether, and the combined ether extracts were washed with water, 5% sodium thiosulphate solution and again with water, and dried over sodium sulphate. The residue after evaporating the ether, 3·4 g, was dehydrated by refluxing for 2 hr with 40 ml of acetic anhydride. The excess of acetic anhydride was removed under reduced pressure and the residue was dissolved in ether, and the extract was washed with 5% sodium hydroxide solution and then with water until neutral. The product obtained after removal of the ether on distillation gave 2·9 g (86 per cent) of *trans*-1:1-diemthyl-4*a*-methyl-6-methoxy-7-*iso*propenylphenanthrene, b.p. 152–155°/0·5 mm, as a light-yellow coloured viscous oil (Found: C, 84·0; H, 9·7. Calc for $C_{21}H_{30}O$: C, 84·5; H, 10·1 per cent).

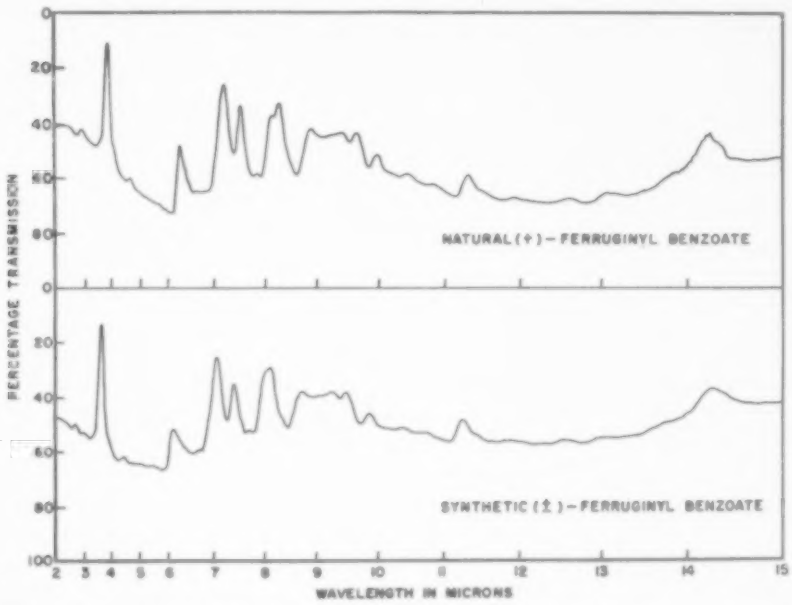
trans-1:1-*Dimethyl*-4a-*methyl*-6-*methoxy*-7-iso*propyl*-1:2:3:4:4a:9:10:10a-*octahydrophenanthrene* (IX). A solution of 2·7 g of *trans*-1:1-dimethyl-4*a*-methyl-6-methoxy-7-*iso*propenyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene in 150 ml of ethanol was hydrogenated in presence of 0·25 g of platinum oxide catalyst at room temperature. After the calculated amount of hydrogen was absorbed the solution was filtered from the catalyst and the alcohol was removed under reduced pressure. The residue on distillation gave 2·6 g of *trans*-1:1-dimethyl-4*a*-methly-6-methoxy-7-*iso*propyl-1:2:3:4:4*a*:9:10:10*a*-octahydrophenanthrene [(±)-ferruginyl methyl ether], b.p. 150–155°/0·8 mm, as a gum having a bluish violet fluorescence (Found: C, 84·1; H, 10·4. Calc. for $C_{21}H_{32}O$: C, 83·9; H, 10·7 per cent).

(±)-*Ferruginol* (X). A mixture of 1·5 g of (IX) and 10 g of pyridine hydrochloride was heated for 5 hr, at 158–160° in an atmosphere of dry nitrogen. Water was added and the product was extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed and the residue was distilled under high vacuum (bath temperature 140–145°/0·5 mm) to give (±)-ferruginol as a pale-yellow resin (Found: C, 83·3; H, 10·4. Calc. for $C_{20}H_{30}O$. C, 83·8; H, 10·6 per cent).

(±)-*Ferruginyl benzoate* (XI). To a solution of 1·2 g of (±)-ferruginol (X) in 10 ml of pyridine, 1 ml of benzoyl chloride was added and the mixture was allowed to stand at room temperature for 2 days. The pyridine was then removed under reduced pressure and the residue was dissolved in ether. The solution was washed with dilute

hydrochloric acid, water, saturated sodium bicarbonate solution and finally with water, and dried over sodium sulphate. The ether was evaporated and the residue was chromatographed on 200 g of neutral alumina of activity II (length of alumina column 30 cm). The fractions eluted with light petroleum (boiling range 40–60°)–benzene (1:1) gave a total of 0·89 g of crystalline material (from methanol), m.p. 118–120°. Two additional crystallisations from ethanol gave analytically pure (±)-ferruginyl benzoate, m.p. 132° (King *et al.*[6] reported 130–130·5°) (Found: C, 83·0 H, 8·8. Calc. for $C_{27}H_{34}O_2$: C, 83·1; H, 8·8 per cent).

The infra-red spectra of the synthetic and natural ferruginyl benzoates were found to be identical in all respects.



The infra-red spectra were recorded in a Nujol mull on a Grubb Parson D.B. 1 type spectrophotometer.

Acknowledgements—We are grateful to Dr. D. K. Banerjee, Head of the Department of Organic Chemistry, Indian Institute of Science, Bangalore, and to Dr. R. C. Shah, Assistant Director, National Chemical Laboratory, Poona, for their interest and encouragement during the course of this investigation. We are much indebted to Dr. F. E. King and to Dr. E. J. T. Grigg for providing us with a sample of natural ferruginyl benzoate.

Our thanks are also due to Dr. G. D. Shah and his associates for the microanalysis and to Dr. Mrs. S. Das Gupta for the infra-red spectra.

Tetrahedron, 1958, Vol. 4, pp. 302–310. Pergamon Press Ltd., London

CUCURBITACIN E: SOME PRELIMINARY OBSERVATIONS

J. N. T. GILBERT and DAVID W. MATHIESON
School of Pharmacy, University of London, Brunswick Square, London

(*Received* 23 *May* 1958)

Abstract—Evidence presented indicates that the functional groupings of cucurbitacin E (α-elaterin) are as follows: an αβ-unsaturated ketone, a 1: 2-diketone (enolised), three hydroxyl groups, one of which is acetylated, and probably a further carbonyl group.

VOL
4
195

α-ELATERIN is a crystalline compound most readily obtained from the fruit juice of squirting cucumber (*Ecballium elaterium*, Rich.). In addition it may be isolated as a glucoside from *Citrullus colocynthis* Schrad. First isolated in 1831 by Morries[1] and also by Hennel,[2] the compound and details of its structure have claimed the attention of a number of investigators.[3–15] More recently α-elaterin has emerged as one member of a group of related compounds provisionally called the cucurbitacins and peculiar to the family Cucurbitaceae.[16–24] Some eleven members (A to L) of this group have been described to date and α-elaterin appears in this list as cucurbitacin E. In what follows preliminary observations on the functional groupings of this substance are presented.

Recent determination of its molecular weight by means of X-ray unit cell and density measurements has allowed the assignment of a revised and probably definitive molecular formula, which suggests that these substances are triterpenoids[24] and the suggested formula $C_{32}H_{44}O_8$ is used in what follows. Elementary analysis agrees with this formula and in addition cucurbitacin E contains one acetoxy group. (From the evidence on functional groupings presented below, it follows as a corollary that cucurbitacin E is pentacyclic.)

[1] Morries, *Edinb. Med. J.* 339 (1831).
[2] H. Hennell, *J. Roy. Instn.* 532 (1831).
[3] C. Zwenger, *Ann. Pharm. Chem.* **43**, 359 (1842).
[4] M. A. Berg, *Bull. Soc. Chim. Fr.* **17**, 85 (1897); **35**, 435 (1906); **7**, 385 (1910).
[5] M. A. Berg, *C.R. Acad. Sci., Paris* **143**, 1161 (1906); **148**, 566 (1909); **150**, 981 (1910).
[6] H. Thoms, *Apoth. Ver.* **44**, 495 (1906).
[7] F. von Hemmelmayr, *Ber. Dtsch. Chem. Ges.* **39**, 3652 (1906).
[8] F. von Hemmelmayr, *Mh. Chem.* **27**, 1167 (1906).
[9] J. Pollak, *Ber. Dtsch. Chem. Ges.* **39**, 3380 (1906).
[10] F. B. Power and C. W. Moore, *Pharm. J.* **83**, 501 (1909).
[11] F. B. Power and C. W. Moore, *J. Chem. Soc.* **95**, 1985 (1909).
[12] C. W. Moore, *J. Chem. Soc.* **97**, 1797 (1910).
[13] Agarwal and Dutt, *Proc. Acad. Sci. Unit. Prov.* 295 (1935).
[14] L. Reichel and K. H. Eisenlohr, *Liebigs Ann.* **531**, 287 (1937).
[15] W. Borsche and K. Diacont, *Liebigs Ann.* **528**, 39 (1937).
[16] P. R. Enslin, *J. Sci. Food Agric.* **5**, 410 (1954).
[17] P. R. Enslin, F. J. Joubert and S. Rehm, *J. S. Afr. Chem. Inst.* **7**, 131 (1954).
[18] P. R. Enslin, F. J. Joubert and S. Rehm, *J. Sci. Food Agric.* **7**, 646 (1956).
[19] P. R. Enslin and D. E. A. Rivett, *J. Chem. Soc.* 3682 (1956).
[20] P. R. Enslin and D. E. A. Rivett, *S. Afr. Industr. Chem.* **11**, 75 (1957).
[21] P. R. Enslin, S. Rehm and D. E. A. Rivett, *J. Sci. Food Agric.* **8**, 673 (1957).
[22] S. Rehm, P. R. Enslin, A. D. J. Meeuse and J. H. Wessels, *J. Sci. Food Agric.* **8**, 679 (1957).
[23] S. Rehm and J. H. Wessels, *J. Sci. Food Agric.* **8**, 687 (1957).
[24] D. E. A. Rivett and F. H. Herbstein, *Chem. & Ind.* 393 (1957).

In the ultra-violet region of the spectrum, cucurbitacin E shews maximum absorption in ethanol at 234 mμ (ϵ 12,500) and 268 mμ (ϵ 8,300). In agreement with previous authors,[19,25] the former band is assigned to an $\alpha\beta$-unsaturated ketone, the latter to an enolised 1:2-diketone. Thus if cucurbitacin E is hydrogenated at a palladium catalyst under conditions under which the double bond of an enone is known to be reduced, the absorption of hydrogen may be stopped at 1 mole. Although the product undergoes secondary changes (viz., loss of acetyl under the action of alkali) and is as yet inadequately characterised, it has lost the former absorption peak at 234 mμ, leaving only that characteristic of the 1:2-diketone. Again, if the spectrum of cucurbitacin E is determined in sodium carbonate solution, the second peak at 268 mμ undergoes a reversible bathochromic shift to 311 mμ (ϵ 5,500) owing to the formation of the enol ion from this 1:2-diketone.[25,26,30] With ferric chloride cucurbitacin E gives a reddish brown coloration, whilst with the benzenediazonium ion a red colour results. The apparent pK_a value for cucurbitacin E, determined spectrophotometrically in 50 per cent ethanol, is 10·8 and the presence of an enol is thus confirmed.

When treated with sodium acetate–acetic anhydride, cucurbitacin E forms an acetyl derivative, which was first described by Hemmelmayr.[8] Two acetyl groups are thus inserted in the molecule. One of these is a normal O-acetyl group, the second forms an enol acetate of the above 1:2-diketone and the acetylcucurbitacin E thus produced shews a high-intensity peak at 233 mμ (ϵ 18,800), the high ϵ value being a summation of the $\alpha\beta$-unsaturated ketone already present and the new $\alpha\beta$-unsaturated carbonyl thus produced by formation of the enol acetate.[30] Unlike cucurbitacin E, the acetate gives no red colour with the benzenediazonium ion. Since, moreover, acetylation produces but a single compound, it would appear that only one of the C atoms adjacent to the 1:2-diketone carries a hydrogen atom. It has been claimed by Lavie[25] that cucurbitacin E forms a quinoxaline: whilst we can confirm that some reaction with *o*-phenylenediamine does occur, the product has so far resisted purification in our hands and no details or physical constants are given by the above author. The amorphous product, however, does shew absorption bands at 238 and 320 mμ characteristic of 2:3-disubstituted quinoxalines[27] and this pattern is not a simple summation of absorption due to cucurbitacin E and *o*-phenylenediamine.

From the infra-red spectrum of cucurbitacin E, bands at 1690 and 1630 cm^{-1} are characteristic, respectively, of the carbonyl group and double bond of the $\alpha\beta$-unsaturated ketone.[28] Bands at 1725 and 1370 cm^{-1} are assigned to the carbonyl and methyl, respectively, of the acetoxy group.[29] A further band in the carbonyl region (1660 cm^{-1}) is not as yet assigned with certainty although probably connected with the 1:2 diketone. It is present in cucurbitacin E and "elateridine" (see below), it is absent both from acetylcucurbitacin E and its glucoside, in which the sugar is likewise attached to the enolic OH.[21] The absence of intense absorption between 1640 and 1530 cm^{-1}, and characteristic of 1:3-diketones,[31] serves to confirm the presence of a 1:2- rather than a 1:3-diketo system. With acetylcucurbitacin E

[25] D. Lavie, *Chem. & Ind.* 466 (1956).
[26] H. S. French and M. E. T. Holden, *J. Amer. Chem. Soc.* **67**, 1239 (1945).
[27] F. Bohlmann, *Chem. Ber.* **84**, 860 (1951).
[28] A. R. H. Cole and D. W. Thornton, *J. Chem. Soc.* 1007 (1956).
[29] R. W. Jones and A. R. H. Cole, *J. Amer. Chem. Soc.* **74**, 5648 (1952).
[30] L. Dorfmann, *Chem. Rev.* **53**, 47 (1953).
[31] R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1068 (1949).

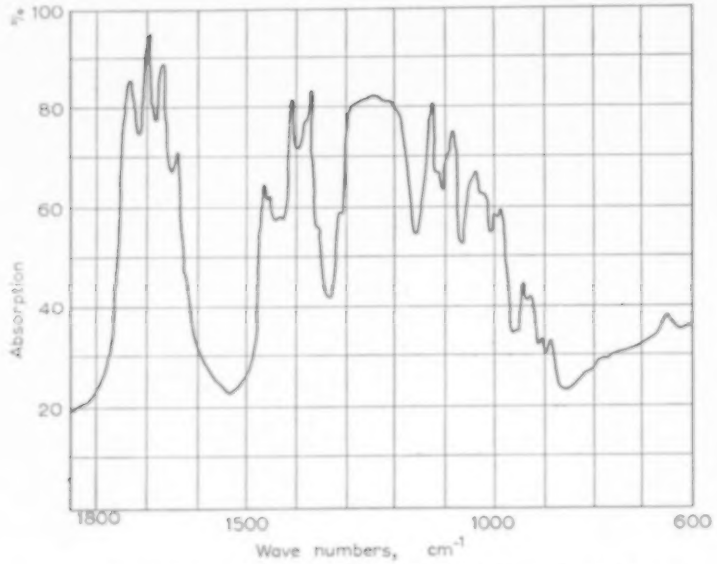


FIG. 1. Infra-red spectrum of cucurbitacin E (2% in chloroform).

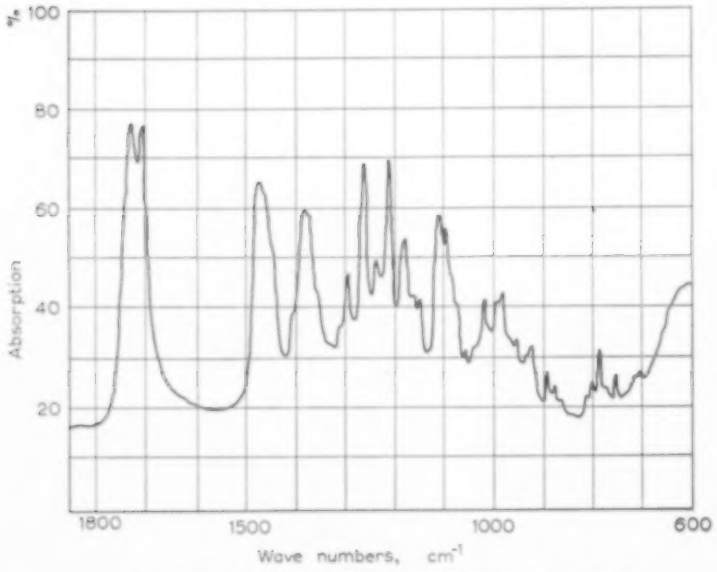


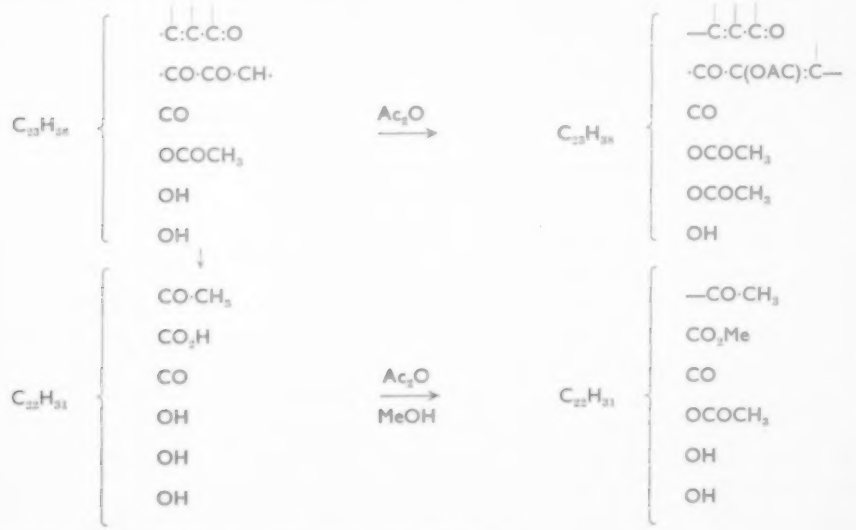
FIG. 2. Infra-red spectrum of methyl ecballate (Nujol mull).

bands at 1770 and 1204 cm^{-1} refer to the enol acetate, whilst those at 1740 and 1240 cm^{-1} are assigned to the two ordinary acetate esters also present. A band at 1370 cm^{-1} due to the C-methyl of these acetate groupings is also observed. An intense band at 1702 cm^{-1} is probably due partly to the carbonyl of the $\alpha\beta$-unsaturated ketones (double bond appears at 1630 cm^{-1}) and partly to a saturated ketone which we believe to be present in addition (see below under ecballic acid).

As stated above, cucurbitacin E contains one hydroxyl group already acetylated. In addition, absorption bands at 3620 and 3546 cm^{-1} and 3468 cm^{-1} correspond, respectively, to free and associated hydroxyl groups. After acetylation, the first two bands disappear and in the acetate there remains but a single peak in this region at 3460 cm^{-1} due to associated hydroxyl.

Active-hydrogen determinations by the method of Zerewitinoff prove difficult in the usual solvents owing to insolubility. Recalculation of previously published determinations[15] carried out in purified quinoline indicates the presence of three active hydrogens in cucurbitacin E and therefore two OH groups in addition to the enolic hydroxyl. We have confirmed this, moreover, by repeating the analysis in N-methyl-1:2:3:4-tetrahydroquinoline as solvent.[32]

Such high concentration of oxygen functions made the action of periodic acid and lead tetra-acetate of obvious interest. When titration of cucurbitacin E with these glycol reagents was carried out, there took place an initial fast consumption of 1 molar equivalent of reagent owing to splitting of the 1:2-diketone. This was followed by a slow continuing uptake. As to acetylcucurbitacin E, only this latter type of slow reaction occurred when periodic acid was used. Lead tetra-acetate had no effect over 3 days. Vicinal hydroxyl functions held in sterically hindered positions are known to shew inactivity towards such reagents,[33,35] and in this connexion it should be noted



[32] G. W. Perold and J. M. Snyman, *Mikrochim. Acta* 225 (1958).
[33] R. Criegee, E. Büchner and W. Walther, *Ber. Dtsch. Chem. Ges.* **73**, 571 (1940).
[34] R. Criegee, L. Kraft and B. Rank, *Liebigs Ann.* **507**, 159 (1933).
[35] O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.* **72**, 1923 (1950).

that one of the hydroxyl groups in cucurbitacin E is inert to acetylation under the usual conditions. Cucurbitacin E does not reduce bismuth trioxide and the absence of the simple grouping —CO—CHOH— may be assumed.

Thus far seven of the eight oxygen atoms may be accounted for.

Action of sodium hydroxide on cucurbitacin E: ecballic acid

When cucurbitacin E is treated with sodium hydroxide at 100°, several changes occur in the molecule and the final product is ecballic acid.[15] With the recent finding that acetoin is split from cucurbitacin E under such conditions[24] the overall changes may be represented thus:

$$C_{32}H_{44}O_8 + 3H_2O \rightarrow C_{26}H_{38}O_7 + CH_3COCHOHCH_3 + CH_3COOH$$

Ecballic acid is a monocarboxylic acid. The approximate pK_a is 4·3 and it contains two ketone groups as shewn by the formation of a bis-2:4-dinitrophenylhydrazone. The isolation of iodoform after oxidation with iodine–sodium hydroxide indicates that one of the carbonyl groups is present as a methyl ketone. Ultra-violet absorption bands characteristic of the $\alpha\beta$-unsaturated ketone and the 1:2-diketone have both disappeared and there remains but low-intensity absorption at 285 mμ (ϵ 112), confirming the presence of the above-mentioned saturated carbonyls.

The second carbonyl group is probably also present in the parent compound, cucurbitacin E, and as such would account for the remaining oxygen function in that molecule.

Methyl ecballate shews bands at 1712 and 1210 cm^{-1} characteristic of the methyl ester.

Thus rearrangement of the two main chromophoric systems of cucurbitacin E has occurred, the $\alpha\beta$-unsaturated ketone having undergone a retroaldol rearrangement, giving rise presumably to acetoin and ecballic acid with its methyl ketone residue. The 1:2-diketone has suffered a benzilic acid type of rearrangement and is the source of the carboxylic acid group. Methyl ecballate forms a monoacetate, which possesses bands at 3612, 3564 cm^{-1} and 3465 cm^{-1} characteristic of free and associated hydroxyl, respectively.

Elateridine

When cucurbitacin E is treated with sodium hydroxide at 20°, an amorphous product results—the so called "elateridine" of Berg.[4] This ill defined intermediate has lost the acetoxy group of the original substance and no longer possesses an absorption band at 234 mμ. Under these conditions only retroaldol rearrangement of the enone system can be envisaged, leaving the 1:2-dione intact. Elateridine thus gives a positive ferric chloride reaction and a red colour with the benzenediazonium ion: it also contains the methyl ketone characteristic of ecballic acid. Infra-red bands at 1695 and 1660 cm^{-1} indicate the enolic form of the 1:2-dione ($\alpha\beta$-unsaturated ketone): the acetate band at 1725 cm^{-1} has disappeared.

When elateridine is treated with sodium hydroxide at 100°, ecballic acid may be obtained.

EXPERIMENTAL

Isolation of cucurbitacin E. Commercial elaterium (180 g) was extracted with light petroleum (boiling range 40–60°) until no further colouring matter was removed.

The marc was then percolated to exhaustion with chloroform. Evaporation of the extract to about 50 ml yielded a crystalline crop, which was filtered off and washed with cold acetone to yield a colourless microcrystalline material (19 g). Several crystallisations from chloroform–methanol yielded pure cucurbitacin E, m.p. 234°, $[\alpha]_D^{20}$ — 64·3° (lit.[14] cites m.p. 234°, $[\alpha]_D$ — 52·9°) (*c*, 1·64 in chloroform) (Found: C, 68·9, 68·6, 68·7; H, 8·2, 8·0, 7·9; 0, 23·9; OAc, 8·02; acetic acid equivalent to three *C*-methyl groups (Kuhn–Roth). Calc. for $C_{32}H_{44}O_8$; C, 69·04; H, 8·0; O, 23·0; OAc, 7·7 per cent). Zerewitinoff determination: cucurbitacin E (22 mg) in N-methyl-1:2:3:4-tetrahydroquinoline was treated with methylmagnesium iodide in di*iso*amyl ether to yield 2·54 ml. of methane (S.T.P.); required for three OH groups, 2·65 ml of methane (S.T.P.).

Light absorption (*a*) in ethanol: 234 mμ (ϵ 12,500), 268 mμ (ϵ 8,300); (*b*) in 0·1 M sodium carbonate: 234 mμ (ϵ 12,500), 311 mμ (ϵ 5,500); (*c*) in 0·1 N sodium hydroxide after 30 hr: 270 mμ (ϵ 3,600), 315 mμ (ϵ 5,700). Infra-red peaks (chloroform solution) at 3620, 3546, 3468, 1725, (330),* 1690 (650), 1660 (390), 1630 (190), 1370 cm^{-1}.

Determination of pK_a *value.* By using standard buffers of known pH prepared in 50% ethanol, the optical density was determined at various wavelengths and the pK_a value was calculated in the usual fashion. The results are shown in Table 1.

TABLE 1. DETERMINATION OF pK_a VALUE

Wavelength (mμ)	$E_{1cm}^{1\%}$ at pH				Calculated pK_a	
	2·3	9·7 (*a*)	10·8 (*b*)	11·5	(*a*)	(*b*)
268	142·3	132	87	40·3	10·65	10·73
280	109·5	101·6	74·3	46·5	10·54	10·7
300	18·3	21·7	49·3	79·1	10·93	10·78
310	9·5	14·5	51·5	91·5	10·89	10·78
320	7·5	12·5	48·7	87·4	10·88	10·77
Mean pK_a value, 10·76						

If $E_1 = E_{1cm}^{1\%}$ of the pure enol (pH 2·3) and $E_2 = E_{1cm}^{1\%}$ of the pure enol ion (pH 11·5) at a given wavelength, then, at any given pH, where E is the observed $E_{1cm}^{1\%}$ at that same wavelength:

$$pK_a = pH - \log_{10} \frac{(E_1 - E)}{(E - E_2)}$$

Isosbestic point $E_{1cm}^{1\%}$ at 289 mμ, 59·5.

Acetylcucurbitacin E. Cucurbitacin E (1 g), fused sodium acetate (1 g) and acetic anhydride (10 ml) were heated together for 1 hr at 100°. After the mixture had been poured into cold sodium carbonate solution, extraction with ether gave a crude product (1·07 g), which crystallised from dry ether in colourless needles, m.p. 121°

* Figures in brackets are intensities as peak apparent molar extinction coefficients. They have not been corrected for finite slit width.

(dec.) (lit.[8] cites m.p. 124°), $[\alpha]_D^{22°}$ −68·6° (*c*, 1·94 in chloroform) (Found: C, 67·53, 67·72; H, 7·19, 7·53; OAc, 23·3. Calc. for $C_{36}H_{48}O_{10}$: C, 67·48; H, 7·55; OAc, 20·13 per cent). Zerewitinoff determination: acetylcucurbitacin E (60 mg) in N-methyl-1:2:3:4-tetrahydroquinoline was treated with methylmagnesium iodide in di*iso*amyl ether to yield after 1 hr 1·14 ml of methane (S.T.P.); required for one OH group, 2·10 ml of methane (S.T.P.).

Light absorption in ethanol; 233 mμ (ϵ 18,800) 320 mμ (ϵ 210). Infra-red peaks (carbon disulphide) 1770, 1740, 1702, 1240, 1204: (chloroform) 3460, 1726 (970), 1697 (940), 1630 (280). Attempts to prepare cucurbitacin E benzoate failed to produce any crystalline material.

Periodic acid oxidation. This was carried out in aqueous methanol with a 0·5 M solution of periodic acid. At various time intervals samples were withdrawn and analysed by the method of Jackson.[26] Simultaneous control experiments omitting only the substance under investigation, were also run. The results are shown in Table 2.

Table 2. Periodic acid oxidations

Substance	No. of moles of HIO_4 used per mole substance				
	6 hr	20 hr	48 hr	72 hr	100 hr
Cucurbitacin E	1·2	1·7	1·8	—	1·96
Acetylcucurbitacin E	0·2	0·4	0·6	0·85	0·96

Lead tetra-acetate oxidations. This was carried out in glacial acetic acid. Unused reagent was estimated by the method outlined by Hockett and McClenahan.[27] The results are shown in Table 3.

Attempted preparation of an oxime or 2:4-dinitrophenylhydrazone of cucurbitacin E led to no crystalline materials. On warming with Brady's reagent at 100° for 20 min, an orange precipitate was obtained, which could not be purified by chromatography on kieselguhr–bentonite. Partial resinification took place on attempted crystallisation. Previous claims for the formation of such carbonyl derivatives as a phenylhydrazone[8] or an oxime[5] seem doubtful.

Attempted preparation of a quinoxaline from cucurbitacin E.[25] *o*-Phenylenediamine (1·4 g) and cucurbitacin E (1 g) were heated to 130° in a current of nitrogen.[28] Excess of *o*-phenylenediamine was removed by vacuum sublimation. The basic residue could not be crystallised and was several times precipitated with water from a solution in methanol. It contained no primary aromatic amino groups. Light absorption in ethanol: 238 mμ ($E_{1cm}^{1\%}$ 621) and 320 mμ ($E_{1cm}^{1\%}$ 181·5).

Hydrogenation of cucurbitacin E. Cucurbitacin E (275 mg) in glacial acetic acid (10 ml) was hydrogenated at a 10% palladium–charcoal catalyst (20 mg). Hydrogen uptake (11 ml) corresponded to an absorption of 1 mole hydrogen per mole of

[26] E. L. Jackson, *Organic Reactions* (Ed. Roger Adams) Vol. II, p. 361. Wiley, New York (1944).
[27] R. C. Hockett and W. S. McClenahan, *J. Amer. Chem. Soc.* **61**, 1667 (1939).
[28] V. A. Petrow and N. W. Starling, *J. Chem. Soc.* 60 (1940).

TABLE 3. LEAD TETRA-ACETATE OXIDATION

Substance	No. of moles of $Pb(OAc)_4$ used per mole substance								
	15 min	30 min	1 hr	2 hr	4 hr	8 hr	22 hr	48 hr	114 hr
Cucurbitacin E	1·13	1·2	1·3	1·4	1·6	1·8	2·4	2·9	3·2

cucurbitacin E. The residue could not be satisfactorily crystallised, owing to continuing loss of acetic acid from the material. It gave a brown colour with ferric chloride and a red colour with the benzenediazonium ion. Light absorption in ethanol: 270 mμ ($E^{1\%}_{1cm}$ 122·5). Acetic acid could be removed completely from this material by filtering through a column of activated alumina. Infra-red peaks on this material (KBr disc): 1696, 1660 cm^{-1}.

Ecballic acid. Cucurbitacin E (5 g) and 0·5 N sodium hydroxide (200 ml) were refluxed (2 hr) in a current of nitrogen. The resulting solution was first extracted with ether to remove neutral by-products then added to excess of 10% sulphuric acid and the insoluble residue (*A*) was filtered off. Ether extraction of the filtrate furnished a cream coloured foam (*B*) (1·98 g). The residue (*A*) was reheated in an identical fashion, to yield a further 1·75 g of a foam corresponding to (*B*), whilst a third treatment of residue *A* yielded 0·47 g.

Recrystallisation of bulked fractions *B* from aqueous methanol yielded ecballic acid in colourless prisms containing one molecule of water of crystallisation, m.p. 254–255° (bubbles at 252°) (lit.[15] cites m.p. 257° with bubbling), $[\alpha]_D^{20}$ — 43° (*c*, 2·37 in ethanol) and —61·6° (*c*, 3·46 in acetone). For a sample dried at 100°/10 mm for 16 hr (Found: C, 67·83, 67·0; H, 8·34, 8·2. Acetic acid equivalent to 3·8 C-methyl groups (Kuhn–Roth). Calc. for $C_{26}H_{38}O_7$: C, 67·51; H, 8·28 per cent). Electrometric titration against 0·02 N sodium hydroxide gave a titration equivalent of 472; pH at half neutralisation was 4.28. Light absorption in ethanol: 285 mμ (ϵ, 112).

Methyl ecballate. Ecballic acid (200 mg) in methanol (5 ml) and concentrated sulphuric acid (2 drops) was refluxed for 18 hr. After dilution with water, the sulphuric acid was neutralised with sodium carbonate. Ether extraction yielded 175 mg of solid, which was recrystallised from dry ether, m.p. 207–210° (lit.[15] m.p. 210°), $[\alpha]_D^{20°}$ —47° (*c*, 2·24 in chloroform) (Found: C, 68·05; H, 8·5; O, 23·8. Calc. for $C_{27}H_{40}O_7$: C, 68·04; H, 8·5; O, 23·5 per cent). Light absorption in ethanol: 286 mμ (ϵ 100). Infra-red peaks (Nujol mull): 1712, 1688; (chloroform solution) 1710 (460), 1692 (610). The same product was obtained by the action of diazomethane on the acid.

Methyl ecballate acetate. Methyl ecballate (500 mg) in dry pyridine (10 ml) and acetic anhydride (2 ml) was allowed to stand (2 days) at room temperature in an atmosphere of nitrogen. After dilution with water and making acid with hydrochloric acid, the aqueous portion was extracted with ether. There thus resulted 560 mg of material, which was chromatographed on neutral alumina (Woelhm) grade II (30 g). The material was placed on the column in 20 per cent benzene in light petroleum (boiling range 60–80°) and elution was carried out through the range of solvents light petroleum–benzene–chloroform. The main band (325 mg) was obtained with benzene–

chloroform and crystallised from dry acetone–light petroleum in flat plates, m.p. 181–182°, $[\alpha]_D$ — 85°. (*c*, 1·56 in chloroform) (Found: C, 67·04; H, 8·02. $C_{29}H_{42}O_8$ requires C, 67·16; H, 8·16 per cent). Infra-red peaks (carbon tetrachloride solution): 3612, 3564, 3465; (chloroform solution) 1723 (653) 1700 (550) cm^{-1}.

n-*Butyl ecballate*. Ecballic acid (250 mg) in *n*-butanol (10 ml) and concentrated sulphuric acid (4 drops) were refluxed for 4 hr. On working up as described above for the methyl ester, there resulted 234 mg, which crystallised from dry ether–light petroleum (boiling range 40–60°) in colourless needles, m.p. 166–167° (Found: C, 69·43; H, 9·1. $C_{30}H_{46}O_7$ requires C, 69·47; H, 8·9 per cent).

Ecballic acid 2:4-*dinitrophenylhydrazone*. Ecballic acid)115 mg) in ethanol (10 ml) was heated at 100° with 2:4-dinitrophenylhydrazine (149 mg) and concentrated sulphuric acid (2 drops). After 15 min the orange precipitate was collected and crystallised from methanol, m.p. 165–175° (gradual decomposition) (Found: C, 55·56; H, 5·7; N, 13·67. $C_{38}H_{46}O_{13}N_8$ requires C, 55·47; H, 5·6; N, 13·6 per cent). Main band in chloroform: 367 mμ (ϵ 43,650).

Oxidation of ecballic acid with sodium hydroxide–iodine. Ecballic acid (198 mg) was dissolved in N sodium hydroxide (20 ml) and an aqueous solution of iodine (5% in potassium iodide) was added with shaking until the iodine was no longer decolourised. After 15 min the precipitated iodoform was filtered off, washed, dried and weighed. Yield 78 mg (40 per cent), m.p. and mixed m.p. 121°.

Elateridine. Cucurbitacin E (250 mg) in ethanol (50 ml) was allowed to stand at room temperature (90 hr) with 2% sodium hydroxide (10 ml). Most of the alcohol was removed under reduced pressure and the residue was diluted with water and then extracted with ether. There resulted a colourless foam (249 mg), which was purified by reprecipitation several times with light petroleum from an ether solution. Light absorption in ethanol: 270 mμ ($E^{1\%}_{1cm}$ 121·6). Infra-red bands (chloroform): 1695, 1660 cm^{-1}.

Acknowledgements—We thank Dr. J. E. Page of Glaxo Laboratories Ltd., for determining the infra-red spectra, which were measured on a Perkin–Elmer model 21 spectrophotometer. The hydroxyl region was kindly examined by Mr. W. Kynaston of the Chemical Research Laboratory, Teddington, the instrument used being a modified Hilger D 209 double-beam spectrometer[29] fitted with a quartz prism for measurements in the 3μ region. Compounds were examined in chloroform and carbon tetrachloride at a path length of 0·5 mm. In addition we are indebted to Mr. R. F. Ransom of Messrs. William Ransom and Sons Ltd., who kindly made available to us much of a small stock of α-Elaterin, which enabled this investigation to be initiated. One of us (J.N.T.G.) also thanks the Pharmaceutical Society of Great Britain for a grant during the tenure of which part of this work was carried out.

[29]J. L. Hales, *J. Sci. Instrum.* **26**, 359 (1949); **30**, 52 (1953).

Tetrahedron, 1958, Vol. 4, pp. 311–324. Pergamon Press Ltd., London

CHEMICAL EXAMINATION OF *TYLOPHORA ASTHMATICA*—II

T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai

Chemistry Department, Presidency College, Madras-5, S. India

(*Received* 24 *May* 1958)

Abstract—Tylophorine has been degraded to a compound, identified as 2:3:6:7-tetramethoxy-9-methylphenanthrene. In conjunction with other degradation results and biogenetic considerations, tylophorine is now formulated as 2:3:6:7-tetramethoxyphenanthro(9:10:6′:7′)indolizidine.

A synthesis of the basic ring system, phenanthro-(9:10:6′:7′)indolizidine, present in tylophorine has been achieved.

In a previous paper[1] it was shown that the alkaloid tylophorine contains a tertiary nitrogen atom common to two rings. Careful repetition of this work has shown that during the second stage Hofmann degradation, the expected product de-N-methyl-tylophorine-methine is accompanied by a nitrogen-free product $C_{24}H_{24}O_5$ yielding a crystalline benzoyl derivative, which in all probability is formed by the replacement of a dimethylamino group by hydroxyl.[2] Application of the Hofmann degradation to de-N-methyl-tylophorinemethine yielded a colourless crystalline product analysing for the formula $C_{24}H_{24}O_4$, m.p. 181–188° and not 152–153° as reported earlier.

The ultra-violet absorption spectra of tylophorine, tylophorinemethine, de-N-methyl-tylophorinemethine and the compound $C_{24}H_{24}O_4$ are closely similar to that of phenanthrene. Tylophorine has no easily reducible unsaturation, but tylophorine-methine can be converted to a quaternary compound. The quaternary iodide, $C_{24}H_{27}O_4N,CH_3I$ is identical with tylophorine *iso*methiodide (vide infra). Reversion of a methine to an inactive form of the quaternary salt from which it is derived has been observed in the case of quinolizidine alkaloids of the canadine type.[3] Such a trans-annular interaction appears to be characteristic of eight, nine and ten-membered rings.[4] It may be concluded that tylophorinemethine has an eight-, nine- or ten-membered ring system, incorporating the nitrogen atom.

Treatment of tylophorine with cyanogen bromide gave a high yield of a bromo-cyanamide ($C_{24}H_{27}O_4N$)$\begin{matrix}\diagup\text{CN}\\ \diagdown\text{Br.}\end{matrix}$ with cleavage of one N—C— bond in the alkaloid. Reduction of the bromocyanamide under a variety of conditions failed to yield any pure product. Treatment of the bromocyanamide with sodium borohydride led only to replacement of the bromine by hydroxyl. The hydroxycyanamide on hydrolysis with sulphuric acid re-generated tylophorine, indicating the presence of a 1:4- or 1:5-amino-alcohol system in the compound. The bromocyanamide reacted readily

* A brief summary of this work was published in *Chem. & Ind.* 1484 (1957).

[1] T. R. Govindachari, B. R. Pai and K. Nagarajan, *J. Chem. Soc.* 2801–2803 (1954).

[2] R. H. F. Manske and H. L. Holmes, *The Alkaloids, Chemistry and Physiology* Vol. IV, p. 152. Academic Press, New York (1954).

[3] F. L. Pyman, *J. Chem. Soc.* **103**, 817 (1913) A. Voss and J. Gadamer, *Arch. Pharm.* **248**, 43 (1910).

[4] N. J. Leonard, R. C. Fox and M. Oki, *J. Amer. Chem. Soc.* **76**, 5708 (1954).

with diethylamine but the diethylaminocyanamide could be hydrolysed only to the urea and no further. The ready cleavage by cyanogen bromide indicates the presence of a benzylamine system in tylophorine and the high reactivity of the bromocyanamide, the presence in it of a $—CH_2Br$ group.[5]

Tylophorine methiodide was converted to an optically inactive *iso*methiodide by boiling with potassium hydroxide solution. That no deep-seated molecular rearrangement had taken place in the reaction was inferred from the superposability of the ultra-violet absorption spectra of the two compounds. The derived *iso*methochloride yields on Emde degradation *iso*dihydrohomotylophorine* and on dehydrogenation with palladised charcoal detetrahydro*iso*dihydrohomotylophorine. The latter has a typical phenanthrene spectrum, is non-basic, and contains a pyrrole ring (positive Ehrlich test). On reduction the original *iso*dihydrohomotylophorine is obtained showing that no alteration in ring size had taken place during dehydrogenation. These experiments establish beyond doubt the presence of a five-membered nitrogen-containing ring tylophorine.

After a Hofmann degradation of *iso*dihydrohomotylophorine the product was oxidised and the acidic fraction esterified with diazomethane giving a mixture of methyl esters. A *mono* ester $C_{21}H_{22}O_6$, m.p. 185–186° and a *diester* $C_{22}H_{22}O_8$, m.p. 246–247° were obtained. The latter on hydrolysis gave a dicarboxylic acid, which was converted to an anhydride under crystallisation conditions. This tendency has been noticed[6] in the case of phenanthrene-9:10-dicarboxylic acids. Attempts at decarboxylation of the dicarboxylic acid under a variety of conditions failed. The mono ester, however, hydrolyses and decarboxylates smoothly to yield a tetramethoxymethylphenanthrene, m.p. 188–189°. The identification of this compound was rendered easier by considering certain biogenetic aspects. Robinson[7] has envisaged the possibility of the phenanthrene ring in cryptopleurine[8] being derived from two phenylalanine units. Tylophorine, a phenanthrene derivative and containing four methoxy groups could conceivably be derived from two DOPA units and ornithine (or equivalent). The decarboxylation product should thus prove to be 2:3:6:7-, or 3:4:6:7-, or 3:4:5:6- or 2:3:5:6-tetramethoxy-9-methylphenanthrene. The first three 9-methylphenanthrenes were synthesised by the method of Buchanan *et al.*[9] from the corresponding 9-carboxylic acids and the 2:3:6:7-tetramethoxy-9-methylphenanthrene was found to be identical with the decarboxylation product m.p. 188–189° (mixed m.p., ultraviolet (Fig. 1) and infra-red spectra). This provides positive evidence about the presence of a phenanthrene ring, the orientation of the methoxy groups and one point of attachment of the heterobicyclic system in tylophorine.

Oxidation of tylophorine methohydroxide in aqueous pyridine with potassium permanganate yields two compounds one of which is considered to be 2:3:6:7-tetramethyoxyphenanthrene-9:10-dicarboxylic acid, the other gives an analysis corresponding to its imide. Vigorous oxidation of tylophorine methiodide with aqueous

* During the course of further degradation experiments (forthcoming publication) it has been shown that this compound is also obtained directly from tylophorine methochloride by Emde degradation.

[5] R. C. Elderfield and M. Green, *J. Org. Chem.* **17**, 431 (1952).

[6] J. Szmuszkovicz and E. J. Modest, *J. Amer. Chem. Soc.* **70**, 2542 (1948); A. Jeanes and R. Adams, *Ibid.* **59**, 2608 (1937).

[7] Sir Robert Robinson, *The Structural Relations of Natural Products* p. 78. Oxford University Press (1955).

[8] E. Gellert and N. V. Riggs, *Aust. J. Chem.* **7**, 113 (1954); J. Friedrichsons and A. Mathieson, *Nature, Lond.* **173**, 732 (1954); E. Gellert, *Aust. J. Chem.* **9**, 489 (1956).

[9] G. L. Buchanan, J. W. Cook and J. D. Loudon, *J. Chem. Soc.* 321 (1944).

potassium permanganate yields *m*-hemipinic acid. The most careful search failed to reveal the presence of any other aromatic acid. Oxidation of tylophorinemethine with potassium permanganate in pyridine yields a neutral, nitrogenous substance, $C_{25}H_{27}O_5N$, apparently formed by the oxidation of a methylene group (adjacent to the nitrogen atom) to a carbonyl group, since reduction with lithium aluminium hydride yielded the original methine.

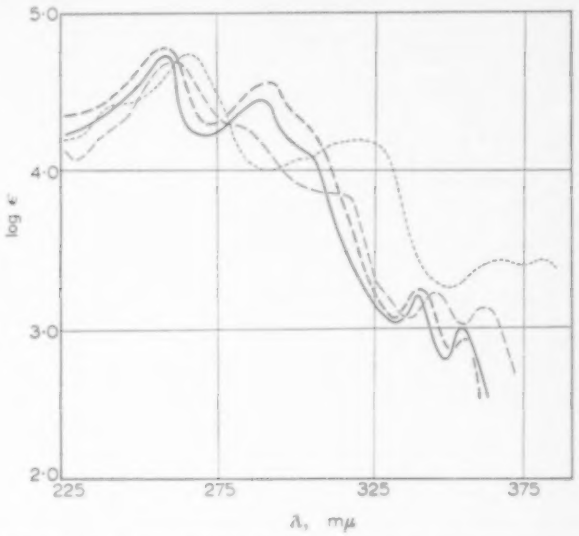


FIG. 1.

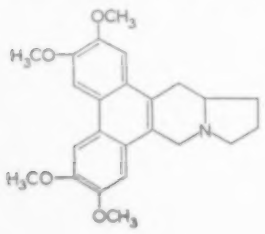
— — Tylophorine

——— 2:3:6:7-Tetramethoxy-9-methylphenanthrene

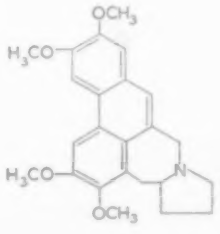
- - - - 3:4:5:6-Tetramethoxy-9-methylphenanthrene

— — 3:4:6:7-Tetramethoxy-9-methylphenanthrene

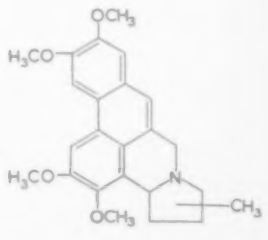
On the basis of the foregoing degradation studies tylophorine can be formulated as 2:3:6:7-tetramethoxyphenanthro(9:10:6′:7′)-indolizidine (I). Although positive evidence that the heterobicyclic system is attached not only to the 9- but also to the 10-position of the phenanthrene ring has not been provided, this is the only structure consistent with biogenetic derivation from DOPA and ornithine and *all* the degradation results. Structures of the type (II) or (III) could also lead to 2:3:6:7-tetramethoxy-9-methylphenanthrene by the sequence employed, but both these structures should yield in addition to *m*-hemipinic acid, a tricarboxylic acid. The methine derived from structure (II) cannot revert to the original quaternary salt. Whilst the methine derived from structure (III) can revert to the original quaternary salt, the structure is inadmissible since tylophorine does not contain a C-methyl group (Kuhn–Roth, infra-red). Both structures (II) and (III) are inconsistent with the biogenetic scheme envisaged.



I

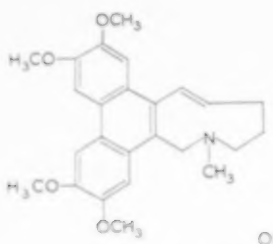


II

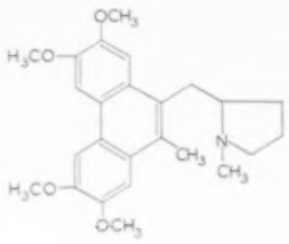


III

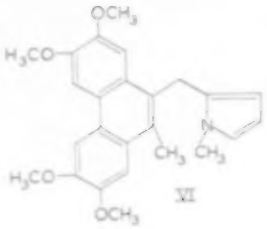
On the basis of structure (I), tylophorinemethine should be (IV), *iso*dihydrohomotylophorine (V) and detetrahydro*iso*dihydrohomotylophorine (VI).



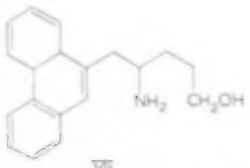
IV



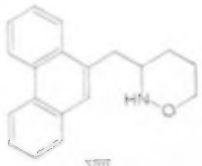
V



VI



VII



VIII

The synthesis of phenanthro(9:10:6′:7′)indolizidine as a model for the synthesis of tylophorine itself has been completed. Phenanthrene-9-aldehyde was condensed with δ-nitrobutyl benzoate. and the resulting nitropentene reduced with lithium aluminium hydride to a mixture of 4-amino-5-(9-phenanthryl)pentanol (VII) and 3-(9-phenanthrylmethyl)-1:2-oxazine (VIII). (VII) was converted to a diformyl derivative which on partial hydrolysis yielded 4-formamido-5-(9-phenanthryl)pentanol. Cyclisation of the latter yielded a quaternary salt which was reduced catalytically to phenanthro(9:10:6′:7′)indolizidine.

EXPERIMENTAL

Hofmann degradation of tylophorine

Tylophorine methiodide (2·5 g) was converted into the methohydroxide and decomposed as described previously.[1] The product was extracted with benzene and filtered. Tylophorinemethine (1·45 g), m.p. 185–188°, $[\alpha]_D^{30} = 0$, was obtained by evaporation of the filtrate. The benzene-insoluble residue (0·4 g) was completely soluble in water and identified as tylophorine *iso*methohydroxide by conversion to the *iso*methiodide, m.p. and mixed m.p., 268–270° (decomp) (Found: C, 56·2; H, 5·9. Calc. for $C_{25}H_{30}O_4NI$; C, 56·1; H, 5·6%). Hofmann degradation of the methine (2 g) was found to give in addition to varying yields of de-N-methyltylophorinemethine (0·15 to 0·75 g), m.p. 177° (with softening above 167°), a nitrogen-free non-basic alcohol (0·65 g), which on crystallisation from methanol, melted indefinitely

at 158–165° (Found: C, 73·5; H, 6·6. $C_{24}H_{25}O_5$ requires C, 73·3; H, 6·4%), but yielded a crystalline *benzoate* (with benzoylchloride in pyridine at 100°), m.p. 188–190° (from methanol) (Found: C, 75·0; H, 6·0 $C_{31}H_{30}O_6$ requires C, 74·7; H, 6·0%). De-N-methyltylophorinemethine methiodide (0·84 g) was converted into the methohydroxide and decomposed *in vacuo*. The product, m.p. 145–150°, was extracted with benzene and shaken with dilute acid. The residue (0·26 g) from the benzene extract was chromatographed over alumina in the same solvent. Elution with benzene gave a colourless *product*, which was crystallised from methanol to give needles, m.p. 181–188° (Found: C, 76·5; H, 6·4; N, 0·0; $C_{24}H_{24}O_4$ requires C, 76·6; H, 6·4%). Benzene containing 0·5% alcohol moved a yellow band. Evaporation gave a pale yellow substance (0·11 g), part (12 mg) of which sublimed at 170–240° at 10^{-5} mm and melted indefinitely at 88–115° (Found: C, 76·0; H, 6·5%). The non-volatile fraction (50 mg) could not be crystallised and had m.p. 230° (decomp; shrinking above 190°) (Found: C, 74·0; H, 7·0; N, 4·4%).

Attempted catalytic reduction of tylophorinemethine

A solution of the methine (0·65 g) in alcohol (100 ml) containing acetic acid (1 ml) was shaken with hyrogen at 60 lb/in² in presence of Adams catalyst (0·1 g) for 6 hr. The solution was filtered, methanol removed *in vacuo*, the residue dissolved in water, and shaken once with benzene. The aqueous acid solution was made alkaline by addition of sodium carbonate, saturated with potassium chloride and extracted with chloroform (1 l.). The solid (0·7 g) recovered from the chloroform extract was recrystallised from alcohol to give *tylophorine* iso*methochloride*, m.p. 208–210° (Found: C, 59·7; H, 7·3. $C_{25}H_{30}O_4NCl$, $3H_2O$ requires C, 60·3; H, 7·2%), identified by conversion to tylophorine isomethiodide, m.p. and mixed m.p. 270–272° (decomp). The use of alcohol alone as solvent for the reduction resulted in recovery of the methine.

Tylophorine bromocyanamide

Tylophorine (1 g) in chloroform (50 ml) was added gradually with stirring to cyanogen bromide (1·5 g) in the same solvent (25 ml) during 2 hr. Next day the solution was evaporated. The residue was ground with dilute acid, filtered and then washed with ammonium hydroxide and water. *The bromocyanamide* (1·05 g) on recrystallisation from benzene melted at 163° (Found: C, 60.4; H, 5·4. $C_{25}H_{27}O_4N_2Br$ requires C, 60·1; H, 5·4%).

Action of sodium borohydride on tylophorine bromocyanamide

The above cyanamide (1·05 g) and sodium borohydride (2·5 g) in methanol (150 ml) were left for 24 hr with occasional shaking. The solution was evaporated *in vacuo* at 30°. The residue was washed with acid and then with water and dried. A benzene solution of the solid was filtered through a column of alumina and the eluate evaporated. Two crystallisations of the solid from methanol gave the *hydroxycyanamide* as a white compound (0·25 g), m.p. 195–198°, with sintering above 187° (Found: C, 68·6; H, 6·7. $C_{25}H_{28}O_5N_2$ requires C, 68·8; H, 6·4%). The hydroxycyanamide (0·25 g) in sulphuric acid (4 N; 5 ml) was refluxed for 3 hr. The clear yellow solution was cooled, shaken once with benzene and then made alkaline. An

initially colourless precipitate which turned yellow was obtained. This had m.p. and mixed m.p. with tylophorine, 283–285° (decomp).

Action of zinc dust on the bromocyanamide

To a warm solution of the bromocyanamide (0·5 g) in acetic acid (50 ml) was gradually added zinc dust (2 g). The mixture was heated to boiling and filtered. The filtrate was evaporated *in vacuo* and the residue dissolved in water and made alkaline. Crystallisation of the precipitate from chloroform–alcohol mixture gave tylophorine, m.p. and mixed m.p. 283–285° (decomp).

Action of diethylamine on tylophorine bromocyanamide

The bromocyanamide (1 g) was refluxed with diethylamine (15 ml) for 3 hr. Excess amine was distilled and the residue taken up in ether and extracted with dilute acid. The acid layer was made alkaline and extracted with ether. Evaporation of the dried (sodium sulphate) ether layer gave a froth (0·88 g), which on crystallisation from methanol gave the *diethylamino-compound* (0·45 g) as colourless thick plates, m.p. 157° (Found: C, 71·0; H, 7·8; N, 8·9. $C_{25}H_{37}O_4N_3$ requires C, 70·9; H, 7·5; N, 8·6%).

Hydrolysis of the diethylamino compound

The above compound (0·5 g) was refluxed with sulphuric acid (20%; 10 ml) for 4 hr. The solution was made alkaline and extracted with ether. The residue (0·27 g) from the ether layer on two crystallisations from aqueous methanol gave the *product*, m.p. 199–200° (decomp) (Found: C, 68·5; H, 7·8; N, 8·4. $C_{20}H_{30}O_5N_2$ requires C, 68·5; H, 7·7; N, 8·3%).

Emde degradation of tylophorine

(a) *Tylophorine* iso*methiodide*. Tylophorine methiodide[1] (3·5 g) was refluxed in methanol (150 ml) and water (150 ml) containing potassium hydroxide (50 g) for 4 hr. The solution was then concentrated to a volume of 100 ml and cooled. The precipitate was filtered and washed with ice-water. Further concentration of the filtrate gave more solid. The combined iso*methiodide* (3·2 g) was recrystallised from water to give white crystals, m.p. 268–270° (decomp), λ_{max} 260, 288, 340, 355 mμ (log ε 4·81, 4·52, 3·39, 3·19) (Found: C, 56·2; H, 5·9. $C_{25}H_{30}O_4NI$ requires C, 56·1; H, 5·6%).

(b) iso*Dihydrohomotylophorine*. The crude *iso*methiodide (3·2 g) was refluxed with silver chloride (from 10 g of silver nitrate) in water (60 ml) and alcohol (60 ml) for 4 hr. The mixture was filtered and the filtrate boiled to remove the alcohol. The aqueous solution of the *iso*methochloride was diluted to 100 ml and heated at 100° with sodium amalgam (5%; 100 g) for several hours, with occasional addition of another 100 g of the amalgam. The crystalline froth was filtered, dried and recrystallised from benzene-petroleum ether (b.p. 40–60°) to yield the *Emde base* (1·4 g), m.p. 200–202°, $[\alpha]_D^{30°}$ ±0°; λ_{max} 260, 290, 340, 360 mμ (log ε 4·80, 4·54, 3·24, 3·12) (Found: C, 72·9; 72·9; H, 7·5, 7·5; N, 3·5; C—CH_3 1·9. $C_{25}H_{31}O_4N$ requires C, 73·4; H, 7·6; N, 3·4; 1 C—CH_3 3·7%).

(c) *de-Tetrahydroisodihydrohomotylophorine*. The Emde base (0·32 g) in *p*-cymene (45 ml) was dehydrogenated with palladium-on-charcoal (0·5 g; 5%) at 220–240°,

till evolution of hydrogen ceased (4 hr). The mixture was filtered and the catalyst washed with benzene. The combined filtrates were evaporated to dryness, the residue ground with dilute hydrochloric acid and filtered. The non-basic residue (0·25 g) was recrystallised from benzene to give *de-tetrahydroisodihydrohomotylophorine* as colourless cubes, m.p. 235°; λ_{max} 255, 290, 340, 355 mμ (log ε 4·79, 4·54, 3·10, 2·90), giving positive pine-splinter and Ehrlich tests (Found: C, 74·2, 74·2 74·0; H, 6·9, 6·6, 6·4; N, 3·2. $C_{25}H_{27}O_4N$ requires C, 74·1; H, 6·7; N, 3·5%).

The above compound (0·1 g) in acetic acid (30 ml) containing Adams catalyst (0·1 g) was shaken with hydrogen at a pressure of 60 lb/in^2 for 7 hr, with addition of more catalyst (0·05 g) at the end of 4 hr. The solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in sulphuric acid (2 N; 10 ml) and shaken with ether. The acid layer was cooled and basified. The precipitate was filtered and washed to give *iso*dihydrohomotylophorine (0·08 g), m.p. and mixed m.p. 198–200°.

Hofmann degradation of iso*dihydrohomotylophorine*

The Emde base (0·95 g) was refluxed with methyl iodide (4 ml) in chloroform (50 ml) for 4 hr and cooled. The precipitate was filtered and washed with chloroform to give the *methiodide* (1·25 g), white cubes (from methanol-ether), m.p. 278–279° (decomp); λ_{max} 260, 290, 340, 355 mμ (log ε 4·85, 4·57, 3·25, 3·02) (Found: C, 56·5; H, 6·1. $C_{26}H_{34}O_4NI$ requires C, 56·6; H, 6·2%). The methiodide (1·2 g) in water (120 ml) was shaken with silver oxide (from 5 g of silver nitrate) for 4 hr. The mixture was filtered and the filtrate evaporated at 50° *in vacuo*. The residue was heated at 100° at 0·5 mm for 1 hr. The product was boiled with benzene, filtered and the filtrate evaporated to give the crude methine (0·5 g), m.p. 127–132° which was chromatographed in benzene through alumina (80 g). After washing with benzene (400 ml) and benzene containing 0·25% ethanol (200 ml), elution with benzene containing 0·75% ethanol (250 ml) gave white crystals, m.p. 136–140°. These were recrystallised from ether to give iso*dihydrohomotylophorinemethine* (0·25 g), m.p. 142° (Found: C, 74·3; H, 7·6. $C_{26}H_{33}O_4N$ requires C, 73·8; H, 7·8%). Further elution of the column with benzene containing 10% ethanol gave a solid (50 mg) which was not further investigated.

Oxidation of iso*dihydrohomotylophorinemethine*

The methine (0·2 g) in acetone (15 ml) was treated gradually with potassium permanganate (1 g) in acetone (200 ml). After 72 hr, the mixture was filtered. The manganese dioxide residue was digested with sodium bicarbonate solution and filtered. The filtrate was extracted with chloroform to remove non-acidic material, concentrated to a small volume and acidified. The precipitated acid (0·1 g) was filtered, suspended in methanol and treated with ethereal diazomethane (from 10 g nitrosomethylurea). After 24 hr the solvents were evaporated and the residue washed with dilute ammonium hydroxide and then with water to give a solid (65 mg), m.p. 180–215°. This was extracted with boiling methanol (10 ml) and filtered. On cooling the methanolic filtrate deposited *methyl 2:3:6:7-tetramethoxy-9-methylphenanthrene-10-carboxylate* (8 mg) as pale yellow cubes, m.p. 185–186°, λ_{max} 260, 290, 340, 358 mμ (log ε 4·75, 4·54, 3·40, 3·15) (Found: C, 68·4; H, 5·8. $C_{21}H_{22}O_6$ requires C, 68·1; H, 5·9%). The methanol-insoluble fraction was recrystallised

twice from benzene to give *dimethyl* 2:3:6:7-*tetramethoxyphenanthrene*-9:10-*dicarboxylate* (8 mg) as pale yellow rectangular plates, m.p. 246–247°, λ_{max} 260, 290, 330 mμ (log ε 4·61, 4·45, 3·80) (Found: C, 63·6; H, 4·9. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·3%). Separation of the two esters (total 150 mg) could also be achieved by chromatography over alumina, the methyl ester (90 mg), m.p. 185–186° being eluted by benzene containing 0·1% methanol and the dimethyl ester (5 mg), m.p. 245–247°, by benzene containing 0·5% methanol. The oxidation of the methine gave the two acids in irreproducible ratio, in most experiments only the dimethyl ester being obtained.

2:3:6:7-*Tetramethoxy*-9-*methylphenanthrene*. The methyl ester, m.p. 186° (50 mg) was refluxed with alcohol (10 ml) and potassium hydroxide (2 g) for 8 hr. As hydrolysis proceeded, the sparingly soluble potassium salt separated. The solvent was evaporated, the residue dissolved in hot water, filtered and the filtrate acidified to give the acid (40 mg), m.p. 225–227°. This was dissolved in quinoline (2 ml) and heated with copper sulphate (20 mg) for 3 hr. Benzene (100 ml) was added to the mixture and the solution washed successively with dilute acid, water, dilute sodium hydroxide and water. The benzene layer was dried (sodium sulphate) and evaporated and the residue filtered in benzene solution through alumina. Evaporation of the eluate and recrystallisation from methanol gave the *methylphenanthrene* (10 mg) as almost colourless needles, m.p. 188–189°, λ_{max} 255, 285, 340, 355 mμ (log ε 4·88, 4·50, 3·20, 2·97), undepressed by admixture with a synthetic specimen (see below).

2:3:6:7-*Tetramethoxyphenanthrene*-9:10-*dicarboxylic acid*

The diester, m.p. 245–247° (0·12 g) was refluxed with potassium hydroxide (2 g) in alcohol (10 ml) for 4 hr. Water (50 ml) was added to the solution which was boiled to remove the alcohol. The cooled aqueous solution was extracted with ether and then acidified. The yellow precipitate (100 mg) was recrystallised from acetic acid or anhydride to give the *anhydride* as yellow needles, which shrank above 290°, and melted indefinitely at 315–325° (decomp) (Found: C, 64·8; H, 4·3. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%).

Oxidation of tylophorine

A suspension of tylophorine (1·3 g) in water (20 ml) was treated with potassium permanganate solution (5%; 210 ml) with stirring and slight warming when the rate of oxidation slackened. The mixture was filtered from the manganese dioxide residue. No acidic material could be recovered from the filtrate. The manganese dioxide residue from the oxidation was extracted with chloroform. The extract was concentrated and passed through an alumina column. Evaporation of the first 100 ml of the eluate gave a colourless solid which on recrystallisation from chloroform-alcohol mixture gave a *substance* (10 mg), colourless needles, m.p. 249° (Found: C, 64·3; H, 5·3. $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4%). Further elution with chloroform gave a solid which crystallised from chloroform-alcohol mixture as deep brown needles (10 mg) of another *substance*, m.p. 253–255° (Found: C, 62·2; H, 5·0; N, 1·2%).

Oxidation of tylophorine iso*methohydroxide*

The *iso*methohydroxide (1 g) in water (25 ml) and pyridine (15 ml) was treated with aqueous potassium permanganate (N/10) first at 30° and then with warming.

Addition of the oxidant was stopped when a faint pink colour persisted. The mixture was filtered and the filtrate evaporated *in vacuo* and acidified. The gum that separated was treated with sodium bicarbonate solution and extracted with ether. The aqueous layer was acidified and the precipitate crystallised from acetic acid to yield the dicarboxylic anhydride (6 mg), m.p. 320–325° (decomp). The manganese dioxide residue from the oxidation was extracted with hot chloroform and the extract washed with dilute acid, dried and evaporated. The residue on crystallisation from acetic acid or pyridine gave 2:3:6:7-*tetramethoxyphenanthrene*-9:10-*dicarboxylimide* (12 mg), m.p. 355° (decomp), with shrinking above 330° (Found: C, 65·0, 64·9; N, 5·2, 5·1; N, 4·0. $C_{20}H_{17}O_6N$ requires C, 65·4; H, 4·6; N, 3·8%).

Oxidation of tylophorine methiodide

Tylophorine methiodide (0·5 g) in water (150 ml) was treated with aqueous potassium permanganate (3%; 130 ml) with stirring at 30° and then at 100° till a faint pink colour persisted. The mixture was filtered and the manganese dioxide residue washed thoroughly with hot water. The filtrate was evaporated to dryness, acidified with dilute sulphuric acid and extracted continuously with ether for 12 hr. The extract was dried (sodium sulphate) and evaporated. The residue from two such batches was sublimed in a high vacuum at 180–200° to give a white sublimate (0·1 g) which was taken up in alcohol (5 ml) containing ethylamine (2 ml). The solution was evaporated and the residue treated again with alcoholic ethylamine. The solvents were evaporated and the residue heated at 180° for 5 min, and sublimed *in vacuo* at 150–200°. The sublimate on one crystallisation from alcohol gave pale yellow needles (30 mg), m.p. 225–227°, with shrinking above 220°. Filtration through an alumina column and a second crystallisation from alcohol gave N-*ethyl*-m-*hemipinimide* (15 mg), as colourless needles, m.p. and mixed m.p. 230–231° (Found: C, 61·4; H, 5·1. Calc. for $C_{12}H_{13}O_4N$ C, 61·3; H, 5·5%). A sample for comparison was prepared by oxidising as before 3:4-dihydro-6:7-dimethoxy*iso*-quinoline (1 g). Treatment of the acidic product (0·55 g) with ethylamine and vacuum sublimation gave N-ethyl-*m*-hemininimide (0·3 g).

Oxidation of tylophorinemethine

(a) *With potassium permanganate.* The methine (0·5 g) in dry pyridine (25 ml) was treated gradually with potassium permanganate (1 g). When no pink colour persisted, the solution was filtered and the filtrate evaporated. The residue was washed successively with acid, alkali and water. The neutral *product* (0·35 g) on crystallisation from benzene–petroleum ether (b.p. 40–60°), had m.p. 241–244°, with partial decomposition above 230° (Found: C, 71·5; H, 6·5; N, 3·5. $C_{25}H_{27}O_5N$ requires C, 71·3; H, 6·4; N, 3·3%), unaffected by refluxing with 20% alcoholic potassium hydroxide. The use of acetone instead of pyridine gave the same product together with partial recovery of the methine, while in aqueous acid solution, no product could be obtained. A solution of the lactam (0·1 g) in tetrahydrofuran (30 ml) reduced with lithium aluminium hydride (0·8 g) gave tylophorinemethine (30 mg) as colourless needles (from benzene–petroleum ether, b.p. 40–60°), m.p. and mixed m.p. 187–188°.

(b) *With alkaline hydrogen peroxide.* The methine (0·7 g) in tetrahydrofuran (50 ml) was made alkaline with a concentrated aqueous solution of sodium hydroxide

and treated with hydrogen peroxide (30%; 365 ml) at 100° with vigorous stirring. The solution was concentrated *in vacuo* to 30 ml and extracted with ether. The aqueous layer was acidified and extracted with ether (10 × 150 ml). The ether layer was evaporated to give an acid (10 mg), which on treatment with ethereal diazomethane and crystallisation of the product from benzene-methanol gave pale yellow needles (2 mg), m.p. 247–248°, undepressed by admixture with dimethyl 2:3:6:7-tetramethoxyphenanthrene-9:10-dicarboxylate reported above.

Syntheses of Tetramethoxymethylphenanthrenes

2:3:6:7-*Tetramethoxy-9-methylphenanthrene*

(a) 3:4-*Dimethoxy-α-(3:4-dimethoxyphenyl)-6-nitrocinnamic acid.* A mixture of 6-nitroveratraldehyde (21 g), homoveratric acid (21 g), acetic anhydride (40 ml) and triethylamine (20 ml) was heated for 16 hr at 100°, protected from moisture. Water (20 ml) was added and the mixture, after remaining for some time, poured into potassium carbonate (160 g) in water (1 l.) and heated till all the gummy material dissolved. The red solution was cooled, shaken with ether (2 × 100 ml) and acidfied with hydrochloric acid. Two crystallisations of the separated gum from methanol gave the *cinnamic acid* (28 g), m.p. 185° (Found: C, 58·3; H, 5·0. $C_{19}H_{19}O_8N$ requires C, 58·6; H, 4·9%).

(b) 2:3:6:7-*Tetramethoxyphenanthrene-9-carboxylic acid.* The above nitro acid (10 g) in ammonium hydroxide (4 N; 180 ml) was added with stirring to a hot mixture of concentrated aqueous ammonia (d 0·88; 180 ml) and ferrous sulphate (75 g) in water (180 ml). After stirring for ¾ hr at 90°, the mixture was filtered. The filtrate was cooled, shaken once with benzene, and then carefully made neutral with concentrated hydrochloric acid. The precipitated amino acid was filtered, washed first with water, then with cold methanol and allowed to dry. To a mixture of the amino acid (3 g) in dioxane (90 ml) and concentrated sulphuric acid (1 ml) at 30° was added dropwise with stirring, freshly prepared *iso*amyl nitrite (2 ml) in dioxane (10 ml). The diazonium solution was added at 40° with stirring to a mixture of freshly precipitated copper (1 g) and sodium hypophosphite (20 g) in water (20 ml) (heated initially to 90° and cooled to 40–50°). The stirring was continued for several hr at 40° and then for 1 hr at 90°. The mixture was then poured into water (1 l) containing sufficient ammonium hydroxide solution to dissolve the acidic product. The mixture was filtered, and the filtrate acidified with concentrated hydrochloric acid. The dark precipitate was collected and boiled with three portions (20 ml) of methanol and filtered. The residue was dissolved in dilute sodium carbonate solution, extracted once with benzene and acidified. Crystallisation of the precipitate from acetic acid gave 2:3:6:7-*tetramethoxyphenanthrene-9-carboxylic acid* (0·4 g), m.p. 285° (Found: C, 66·7; H, 5·3. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%). The methanolic filtrate was evaporated and the residue recrystallised from acetone, to give 3:4:6:7-*tetramethoxyphenanthrene-10-carboxylic acid* (0·3 g) m.p. 210° (Found: C, 66·7; H, 5·3%), which on decarboxylation by a procedure similar to that described below, gave 3:4:6:7-tetramethoxyphenanthrene, m.p. and mixed m.p. with an authentic sample, 121°.

(c) 2:3:6:7-*Tetramethoxyphenanthrene.* The acid, m.p. 285° (0·1 g), from the above experiment was refluxed in quinoline (3 ml) in the presence of copper sulphate

(0·1 g) for 1 hr. The mixture was cooled, poured into excess hydrochloric acid and extracted with benzene (3 × 25 ml). The benzene extract was washed with dilute alkali and water. The dried (sodium sulphate) extract gave on evaporation and crystallisation of the residue from methanol, the *phenanthrene* (30 mg), m.p. 178°, λ_{max} 255, 285, 300, 335, 350 mμ (log ε 4·86, 4·38, 4·16, 3·08, 2·78) (Found: C, 72·4; H, 6·1. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%).

(d) *Methyl* 2:3:6:7-*tetramethoxyphenanthrene*-9-*carboxylate*. The acid (2 g) in methanol (20 ml) was treated during 24 hr with ethereal diazomethane (from 20 g of nitrosomethylurea), to give as the neutral product, the *methyl ester* (1·8 g) which crystallised from alcohol had m.p. 195° (Found: C, 67·7; H, 5·4. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%).

(e) 2:3:6:7-*Tetramethoxyphenanthrene*-9-*carboxylic acid hydrazide*. The foregoing ester (0·5 g), hydrazine hydrate (85%; 1·5 ml) and *iso*amyl alcohol (5 ml) were refluxed for 4 hr, cooled and treated with mehtanol (20 ml). The solid was crystallised from ethanol to give the *hydrazide* (0·3 g), m.p. 246° (decomp) (Found: C, 63·9; H, 5·8. $C_{19}H_{20}N_2O_5$ requires C, 64·0; H, 5·6%). The hydrazide (0·3 g), dried at 140° *in vacuo*, was left in pyridine solution (10 ml) with benzenesulphonyl chloride (0·4 g) at 0° for 24 hr, and poured into ice and hydrochloric acid. The precipitate was recrystallised from acetone–methanol to give the *benzenesulphonyl derivative* (0·2 g), m.p. 265° (decomp) (Found: C, 60·4; H, 4·6. $C_{25}H_{24}N_2SO_7$ requires C, 60·5; H, 4·8%).

(f) 2:3:6:7-*Tetramethoxyphenanthrene*-9-*aldehyde*. The above sulphonyl derivative (0·2 g) dried at 140° *in vacuo* was treated in ethylene glycol solution (10 ml) at 160° with anhydrous sodium carbonate (0·2 g). After 80 sec, warm water was added. The mixture was cooled and extracted with chloroform. The chloroform layer was washed with water, dried (sodium sulphate) and evaporated and the residue crystallised from acetic acid giving the *aldehyde* (0·15 g), m.p. 210° (Found: C, 69·6; H, 5·3. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

(g) 2:3:6:7-*Tetramethoxy*-9-*methylphenanthrene*. The foregoing aldehyde (0·1 g) was refluxed with hydrazine hydrate (85%; 1 ml) in absolute alcohol (5 ml) for 2 hr. The solvent was removed *in vacuo*. Powdered potassium hydroxide (0·2 g) was added to the residue which was then heated at 190° for ½ hr. Water (10 ml) was added and the solid product extracted with benzene. The benzene extract was washed with water, dried (sodium sulphate), evaporated and the residue sublimed *in vacuo*. Recrystallisation of the sublimate from methanol gave 9-*methylphenanthrene* (20 mg), m.p. 188–189° λ_{max} 255, 285, 340, 355 mμ (log ε 4·74, 4·41, 3·19, 2·99) (Found: C, 72·8; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%).

3:4:5:6-*Tetramethoxy*-9-*methylphenanthrene*

(a) *Methyl* 3:4:5:6-*tetramethyoxyphenanthrene*-9-*carboxylate*. 2-Amino-α-(6-bromo-3:4-dimethoxyphenyl)-3:4-dimethoxycinnamic acid[10] (11 g) was diazotised with *iso*amyl nitrite (6 ml) and treated with sodium hypophosphite-copper mixture to give the crude acidic product (5 g). Repeated fractional crystallisation from methanol gave as the more soluble fraction, 8-*bromo*-3:4:5:6-*tetramethoxyphenanthrene*-9-*carboxylic acid* (1 g), m.p. 187° and 3:4:5:6-*tetramethoxyphenanthrene*-9-*carboxylic acid* (2 g), m.p. 236° as the less soluble fraction. This acid (2·5 g) was refluxed for

[10] H. Kondo and E. Ochiai, *Liebigs Ann.* **470**, 224 (1929).

2 hr with dry methanol (25 ml) containing concentrated sulphuric acid (1 ml). The methanol was distilled and water was added to the residue, which was then extracted with chloroform. The chloroform layer was washed with sodium carbonate solution and water, and dried (sodium sulphate) and evaporated. The residual gum crystallised from dilute alcohol to give the *methyl ester* (1·5 g), m.p. 70° (Found: C, 67·6; H, 5·3%).

(b) 3:4:5:6-*Tetramethoxyphenanthrene*-9-*carboxylic acid hydrazide*. The ester (1·5 g) was refluxed with hydrazine hydrate (64%; 15 ml) in absolute alcohol (15 ml) for 4 hr, to yield the *hydrazide* (1·3 g), m.p. 175° (from benzene) (Found: C, 61·0; H, 6·0. $C_{19}H_{20}N_2O_5 \cdot H_2O$ requires C, 61·0; H, 5·9%).

(c) N-*Benzenesulphonyl*-3:4:5:6-*tetramethoxyphenanthrene*-9-*carboxylic acid hydrazide*. The benzenesulphonyl derivative (0·7 g) from 1·1 g of hydrazide, with 0·6 ml benzenesulphonyl chloride in pyridine (15 ml) crystallised from alcohol and had m.p. 217° (Found: C, 60·3; H, 5·2%).

(d) 3:4:5:6-*Tetramethoxyphenanthrene*-9-*aldehyde*. The foregoing benzensulphonyl derivative (0·7 g) was rearranged as previously, in ethylene glycol solution (25 ml) with sodium carbonate (0·6 g), to yield the *aldehyde* (0·3 g), m.p. 127° (from alcohol) (Found: C, 69·9; H, 5·5%).

(e) 3:4:5:6-*Tetramethoxy*-9-*methylphenanthrene*. The foregoing aldehyde (0·3 g), anhydrous hydrazine (0·6 ml) and absolute alcohol (6 ml) were refluxed for 2 hr and the solvent removed *in vacuo*. Powdered potassium hydroxide (0·3 g) was added to the residue maintained at 120–125°. After 25 min, water was added and the suspension extracted with ether. The residue from the ether extract was filtered through an alumina column, in benzene solution and the product obtained by evaporation of the benzene was crystallised from methanol to give 3:4:5:6-*tetramethoxy*-9-*methylphenanthrene* (80 mg), m.p. 87–88°, λ_{max} 265, 310, 325, 368, 380 mμ (log ε 4·73, 4·16, 4·16, 3·41, 3·43) (Found: C, 72·9; H, 6·5%).

3:4:6:7-*Tetramethoxy*-9-*methylphenanthrene*

3:4:6:7-Tetramethoxyphenanthrene-9-carboxylic acid (2·5 g), m.p. 210° was obtained by subjecting 2-amino-α-(3:4-dimethoxyphenyl)-3:4-dimethoxycinnamic acid[10] (15 g) to the Pschorr reaction. The *ethyl ester*, made as usual had m.p. 105° (Found: C, 68·0; H, 5·9. $C_{21}H_{22}O_6$ requires C, 68·1; H, 6·0%). This was converted into the *hydrazide* (0·5 g from 0·6 g ester), m.p. 219° (from alcohol) (Found: C, 64·0; H, 5·8%), thence into the *benzenesulphonyl derivative* (0·2 g from 0·4 g hydrazide), m.p. 245° (from alcohol-dioxane) (Found: C, 60·6; H, 5·0%). This was rearranged as before into 3:4:6:7-*tetramethoxyphenanthrene*-9-*aldehyde* (0·1 g) which, on crystallisation from alcohol, melted at 148° (Found: C, 69·6; H, 5·3%), which was then reduced by the usual Wolff–Kishner method to give 3:4:6:7-*tetramethoxy*-9-*methylphenanthrene*, m.p. 123° (from methanol), λ_{max} 260, 315, 345, 360 mμ (log ε 4·70, 3·86, 3·21, 3·10) (Found: C, 72·7; H, 6·3%).

Phenanthro(9:10:6′:7′)*indolizidine*

(a) δ-*Nitrobutyl benzoate*

Powdered silver nitrite (48 g) was added, with stirring, at 70–80°, to δ-bromobutyl benzoate[11] (78 g) in the course of 5 hr. The reaction mixture was heated for 4 hr,

[11] J. B. Cloke and F. J. Pilgrim, *J. Amer. Chem. Soc.* **61**, 2667 (1939).

cooled and the product taken up in ether, was filtered from silver bromide. The ether was evaporated and the residue fractionated twice under reduced pressure (metal or oil bath for heating) and the fraction distilling at 156–157°/1·5 mm collected (Found: C, 59·0; H, 6·0. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8%).

(b) *5-Benzoyloxy-2-nitro-1-(9-phenanthryl)-Δ′-pentene*

Phenanthrene-9-aldehyde (10 g), δ-nitrobutyl benzoate (10 ml) and ammonium acetate (5 g) were refluxed in acetic acid (60 ml) for 2 hr. The red solution was poured into water, and the heavy oil that separated was washed several times with water and mixed with ethanol. The solid that separated was filtered and recrystallised from alcohol and had m.p. 118° (Found: C, 76·3; H, 5·3. $C_{26}H_{21}O_4N$ requires C, 75·9; H, 5·1%).

(c) *4-Amino-5-(9-phenanthryl)pentanol*

(i) *By electrolytic reduction of* (b). A mixture of the foregoing nitropentene (5 g), acetic acid (200 ml), ethanol (50 ml) and concentrated hydrochloric acid (15 ml) was placed in the cathode compartment and dilute sulphuric acid (20%) in the anode compartment, maintaining the level of the anolyte slightly higher than that of the catholyte. Using lead electrodes, a steady current of 5 amperes was passed continually for 18 hr, while the catholyte was stirred. The catholyte was filtered and evaporated *in vacuo*; the residue was ground well with aqueous ammonia and the basic material taken up in ether. The ether was removed and the residue refluxed with dilute sulphuric acid (4 N; 70 ml) for 2 hr. The cooled acid solution was shaken with ether and then basified with ammonia. The base was extracted with ether and purified by crystallisation from benzene; it melted at 120° (Found: C, 81·6; H, 7·4; N, 5·0. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%).

The *picrate* made as usual had m.p. 175° (from alcohol). (Found: C, 59·3; H, 4·9; N, 11·3. $C_{25}H_{24}O_8N_4$ requires C, 59·1; H, 4·7; N, 11·0%).

(ii) *By lithium aluminium hydride reduction of* (b). A solution of the nitropentene (8·5 g) in dry tetrahydrofuran (50 ml) was added with stirring to a suspension of lithium aluminium hydride (3 g) in tetrahydrofuran (30 ml) kept protected from moisture. After decomposing with water, the tetrahydrofuran solution was filtered and concentrated almost to dryness. Ether was added and the solution cooled to 10°. The solid that separated was filtered and recrystallised from benzene to give *3-(9-phenanthrylmethyl)-1:2-oxazine* (1·2 g), m.p. 185° (λ_{max} 255, 300, 350, mμ log ε 4·73, 4·03, 2·56) (Found: C, 82·4; H, 6·9; N, 5·2. $C_{19}H_{19}ON$ requires C, 82·3; H, 6·9; N, 5·0%).

The mother liquor after separation of the oxazine, was left at 0° overnight. The solid that separated from it was recrystallised from benzene and had m.p. 120° and it was identical with the electrolytic reduction product. The amino-alcohol gave a *monobenzoyl derivative*, m.p. 155° (from benzene) (Found: C, 81·7; H, 6·5. $C_{26}H_{25}O_2N$ requires C, 81·5; H, 6·5%).

(d) *4-Formamido-5-(9-phenanthryl)pentanol*

The amino-alcohol (1 g), was heated with formic acid (98%; 3 ml) at 180° for 2 hr. The neutral product isolated, was recrystallised from benzene to give the O:N-*diformyl derivative* (1 g), m.p. 145° (Found: C, 75·3; H, 6·4; N, 3·9. $C_{21}H_{21}O_3N$

requires C, 75·2; H, 6·0; N, 4·2%). This was refluxed with aqueous sodium hydroxide (10%; 10 ml) for 1 hr. The gum that separated was washed well with water and mixed with benzene to give a solid, which was recrystallised from a very large volume of benzene giving the *N-formyl compound* (0·6 g), m.p. 150° (Found: C, 77·9; H, 6·9. $C_{20}H_{21}O_2N$ requires C, 78·2; H, 7·0%).

(c) *Phenanthro*(9:10·6′:7′)*indolizidine*

The foregoing monoformyl derivative (0·5 g) was refluxed for 1 hr with phosphorus oxychloride (5 ml) in sulphur-free dry toluene (5 ml). The toluene layer was diluted with a large excess of dry petroleum ether. The gummy material was washed well with dry petroleum ether, and then extracted with hot water. The aqueous extract was cooled, neutralised and treated with excess potassium iodide to give the quaternary iodide (0·2 g), which was separated, washed and reduced catalytically in methanolic suspension using Adams catalyst (50 mg) at a hydrogen pressure of 50 lb/in². The catalyst was filtered, the solvent removed and the residue ground with alkali and extracted with chloroform. After removal of the chloroform the residue was recrystallised from methanol to give *phenanthro*(9:10:6′:7′)*indolizidine* (50 mg), m.p. 170°, λ_{max} 255, 270, 300, 335, 340, 350 mμ (log ε 4·73, 4·56, 3·98 2·6, 2·6, 2·68) (Found: C, 87·8; H, 6·8. $C_{20}H_{19}N$ requires C, 87·9; H, 6·9%).

We thank Sir Alexander Todd, F.R.S., and Dr. N. Sheppard for infra-red data; Mr. S. Selvavinayagam for the microanalyses; and the Government of India for a Scholarship (to M. V. L.). We are grateful to the Council of Scientific and Industrial Research, India, for financial assistance.

Tetrahedron, 1958, Vol. 4, pp. 325–336. Pergamon Press Ltd., London

STEREOCHEMISTRY OF THE CO-OXIDATION PRODUCTS OF INDENE AND THIOPHENOL

J. F. FORD, R. C. PITKETHLY and V. O. YOUNG
The British Petroleum Co. Ltd., Research Station, Sunbury-on-Thames, Middlesex

(*Received* 1 *March* 1958; *in revised form* 24 *May* 1958)

Abstract—The major primary product of the co-oxidation of indene and thiophenol is *trans*-2-phenylmercapto-1-indanyl hydroperoxide, which spontaneously rearranges to the two racemes of *trans*-2-phenylsulphinyl-1-indanol. Attack by the phenylmercaptyl radical on the indene molecule is, within 5 per cent, exclusively at the 2-position and subsequent addition of oxygen to the intermediate 2-phenylmercaptoindanyl radical is, within the same limits, exclusively a *trans*-addition.

The *cis*- and *trans*-2-phenylmercapto-1-indanols and the related sulphoxides and sulphones have been synthesised. Under certain conditions, the substitution reaction of thiophenate ion with indene bromohydrin is accompanied by migration of the hydroxyl group and production of *trans*-1-phenylmercapto-2-indanol; the sulphoxides and sulphone in this series are also described.

No completely satisfactory interpretation of the stereochemical course of addition of free radicals to olefins has yet been achieved, perhaps because the number of such reactions which have been adequately studied is limited. The results reported here contribute to this subject new experimental data obtained during an investigation of the products of co-oxidation of indene and thiophenol, a model system which simulates in certain ways the behaviour of unstable gum-forming petroleum products derived from catalytic cracking processes.

Kharasch *et al.*[1] identified hydroxysulphoxides as the products of aerial co-oxidation of styrene and other olefins with mercaptans and suggested that hydroperoxides (or peroxy radicals) formed in a free-radical chain constituted intermediates which subsequently underwent rearrangement.

With indene and thiophenol in benzene solution a hydroperoxide is the major primary product of oxidation and the rearrangement to hydroxysulphoxides can be experimentally observed. The syntheses described later in this paper provide reference compounds for the identification of the co-oxidation products and elucidation of their stereochemical configuration.

Co-oxidation of indene and thiophenol

In benzene solution at 20°, the co-oxidation reaction involved indene, thiophenol and oxygen in the molar ratios 1 : 1·06 : 1 and at the end of the reaction 77 per cent of the absorbed oxygen was present as hydroperoxide, which subsequently underwent rearrangement. After complete decay of the hydroperoxide, 85 per cent of the oxygen was found to be present in the two *trans*-2-phenylsulphinyl-1-indanols [(Va) and (Vb)] and 1 per cent in *trans*-2-phenylmercapto-1-indanol (III). With such high yields the precursor of the hydroxysulphoxides must be the hydroperoxide, which, therefore, has the structure (XVI). Confirmation was obtained by lithium aluminium hydride reduction of the peroxide to *trans*-2-phenylmercapto-1-indanol (III).

[1] M. S. Kharasch, W. Nudenberg and C. J. Mantell, *J. Org. Chem.* **16**, 524 (1951).

Although the oxygen accounted for in compounds of completely determined configuration amounts to only 86 per cent of that reacted, it is possible for three reasons to draw conclusions regarding the stereochemistry of this reaction from the yields of hydroxysulphoxides. First, in the rearrangement reaction, 96·7 per cent of the hydroperoxide is converted to hydroxysulphoxides. Secondly, the stereochemical configurations of *cis*- and *trans*-hydroperoxysulphides are such that, although close approach of oxygen and sulphur atoms is possible in the *trans* form, the sulphur atom actually interferes with the rotation of the hydroperoxy group in the *cis* form, which should therefore have an even greater probability of rearrangement to the stable hydroxysulphoxides. Thirdly, when a paraffinic solvent (e.g. 2:2:4-trimethylpentane) is employed, the hydroxysulphoxides (Va) and (Vb) are rapidly formed and precipitated, but none of the isomers (VIa), (VIb), (XIIa) and (XIIb) nor carbonyl absorption could be detected in the infra-red spectrum of the product.

The only fraction having a spectrum resembling those of the *cis*-hydroxysulphoxides [(VIa) and (VIb)] was separated by chromatography and amounted to 0·25 per cent of the total product (0·27 per cent of the absorbed oxygen); no trace of the *cis*-hydroxysulphide (IV) was found. Of the hydroxysulphoxides isolated, 95 per cent have been fully identified as *trans*-2-phenylsulphinyl-1-indanols in the pure state by m.p. and infra-red spectra or, in admixture with one another by spectra and oxidation to the *trans*-hydroxysulphone (VII). The remaining 5 per cent were obtained as chromatograph fractions examined only by infra-red absorption, which could detect the presence of 5 per cent of (VIa) or (VIb) and 2 per cent of (XIIa) or (XIIb) in the mixture of (Va) and (Vb). Therefore, allowing for the 3·3 per cent loss to by-products in the rearrangement reaction and the possible uncertainties in the infra-red examinations, it may be concluded that, within 5 per cent, the attack of the phenylmercaptyl radical on the indene molecule is exclusively at the 2-position and that addition of oxygen to the phenylmercaptoindanyl radical in the second step of the chain reaction occurs *trans* to the phenylmercapto-group:

(XVI)

The orientation of the initial attack is the same as in styrene[1] and can be related to the stabilising effect of the adjacent aromatic ring in the 1-indanyl radical.[2,3]

No completely satisfactory theory of free-radical addition to olefins has yet been developed, but, if the interpretation of Goering *et al.*[4,5] is applicable, the essentially

[2] R. L. Huang, *J. Chem. Soc.* 1749 (1956).
[3] M. Takahasi, *Bull. Chem. Soc. Japan* **29**, 511 (1956); quoted by H. B. Henbest, *Ann. Rep. Chem. Soc.* **53**, 149 (1956).
[4] H. L. Goering, D. I. Relyea and D. W. Larsen, *J. Amer. Chem. Soc.* **78**, 348 (1956).
[5] H. L. Goering and L. L. Sims, *J. Amer. Chem. Soc.* **77**, 3465 (1955).

trans configuration of the product may be attributed to axial attack on the planar indene molecule in the first step, followed by rapid addition of oxygen in the second step before conformational rearrangement can occur. However, evidence to support this view is lacking.

The stereospecificity of free-radical addition reactions can vary in different systems from purely *trans* additions[6–13] at one extreme, through various intermediate degrees of specificity[4,14] to the other extreme in which *cis* and *trans* additions are equally probable.[15,16,17] This sensitivity to structure and conditions is particularly apparent in a comparison of the co-oxidation of indene and thiophenol with the formation of polymeric indene peroxide.[16] Although the second stages of these two reactions are identical, the latter shows no stereospecificity, while the former is a virtually pure *trans* addition. This implies, in the conformational analysis, that the rate of oxygen addition must be slow compared with the conformational rearrangement in the formation of indene peroxide, but relatively fast (as mentioned above) for the co-oxidation reaction. Unfortunately no data is available on the rates of oxygen addition, because this step is usually not rate-determining in either reaction and the control or measurement of radical concentrations is difficult.

Syntheses in the 2-phenylmercapto-1-indanol series

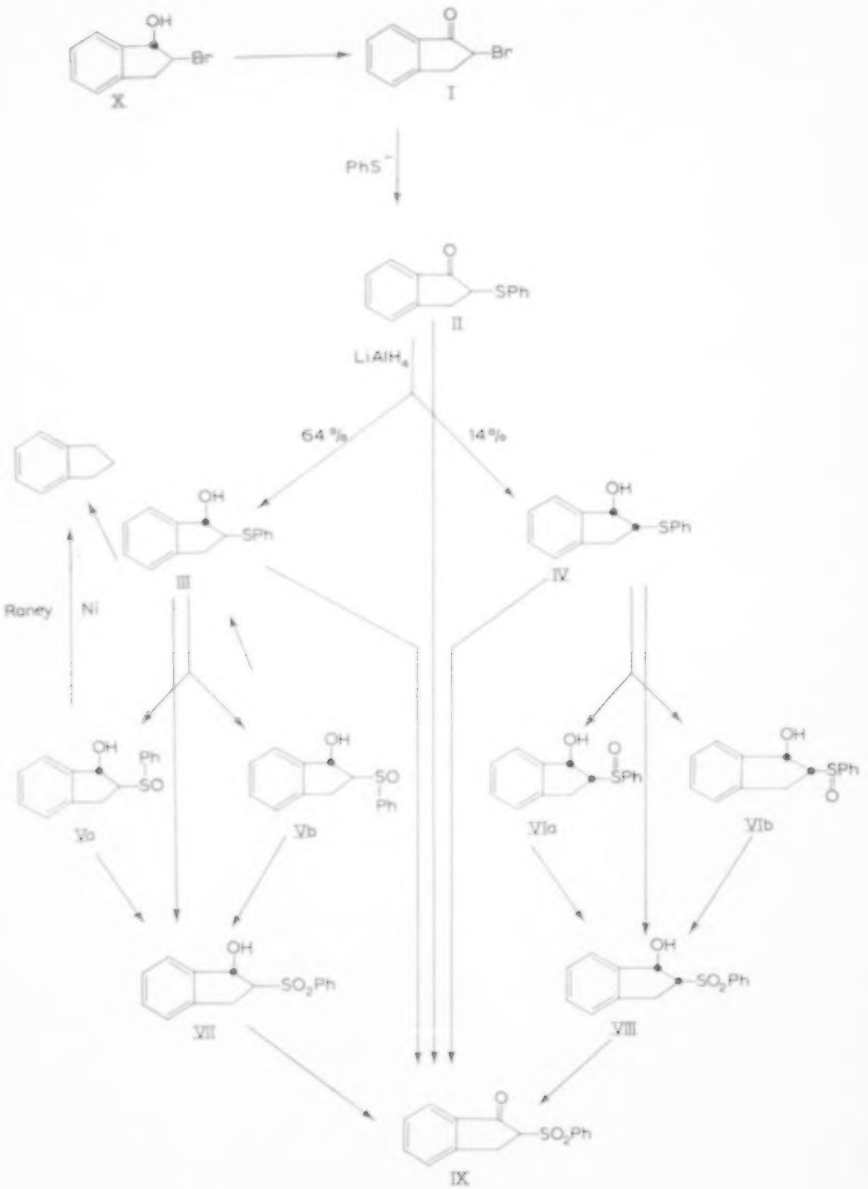
2-Bromo-1-indanone (I) has been previously prepared by chromic acid oxidation of indene bromohydrin[18,19] and also by bromination of 1-indanone;[20] the structure is therefore well established. Replacement of bromine in (I) by the phenylmercapto-group was straightforward and yielded (II); rearrangement at this stage was most improbable.

Reduction of (II) with lithium aluminium hydride was practically quantitative, yielding a separable mixture of the *trans*- and *cis*-2-phenylmercapto-1-indanols [(III) and (IV)] in the ratio of 4·6 : 1. It was shown that isomer (IV) was unaffected by lithium aluminium hydride under the conditions of the reduction and it is evident that the formation of (III) is favoured, but not through an equilibrium with (IV). The preferential production of (III) must therefore be the result of steric influences and this isomer should be the *trans* form, because approach of the large aluminium complex will be less hindered by the C_6H_5S-group if the attack on the oxygen is made from the opposite side of the molecule.[21]

(6) M. S. Kharasch, J. S. Sallo and W. Nudenberg, *J. Org. Chem.* **21**, 129 (1956).
(7) P. I. Abell, B. F. Aycock and H. L. Goering, *J. Amer. Chem. Soc.* **74**, 3588 (1952).
(8) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.* **14**, 239 (1949).
(9) E. S. Fawcett, *Chem. Rev.* **47**, 219 (1950).
(10) J. Weinstock, Abstr. of Papers 128th Meeting of the American Chemical Society, Minneapolis, Sept. 1955, 0. 19–0.
(11) R. H. Rosenwald, *Symposium on the Use of Additives in Petroleum Fuels*. Division of Petroleum Chemistry, American Chemical Society Meeting, Minneapolis, Sept. 1955.
(12) G. M. Bristow and F. S. Dainton, *Proc. Roy. Soc.* A **229**, 509, 525 (1955).
(13) L. K. J. Tong and W. O. Kenyon, *J. Amer. Chem. Soc.* **71**, 1925 (1949).
(14) F. G. Bordwell and W. A. Hewett, Abstr. of Papers, 126th Meeting of the American Chemical Society, Sept. 1954, p. 6–0.
(15) R. Reimenschneider, *Mh. Chem.* **85**, 1133 (1954).
(16) G. A. Russell, *J. Amer. Chem. Soc.* **78**, 1035 (1956).
(17) S. Winstein and D. Seymour, *J. Amer. Chem. Soc.* **68**, 119 (1946).
(18) C. Courtot, Fayet and Parant, *C. R. Acad. Sci., Paris* **186**, 371 (1928).
(19) F. Ishiwara, *J. Prakt. Chem.* [2], **108**, 194 (1924).
(20) F. S. Kipping, *J. Chem. Soc.* **65**, 480, 500 (1894).
(21) N. L. Paddock, *Chem. & Ind.* 63 (1953).

Attempts were made to prove the *cis–trans* relationship of (III) and (IV) by isomerisation with alkali, but without success. However, proof was obtained by oxidation in stages and isolation of the theoretically required number of isomers at each stage, finally ending with one ketosulphone.

Thus, oxidation of (III) with peracetic acid yielded a pair of *trans*-hydroxysulphoxides [(Va) and (Vb)], differing only in the orientation about the sulphur atom; similarly, oxidation of (IV) yielded the pair of *cis*-hydroxysulphoxides [(VIa) and



(VIb)]. The relationship between these four isomers with respect to the orientation about the sulphur atom is not known. Further oxidation gave two hydroxysulphones [(VII) and (VIII)], whose *cis–trans* relationship was confirmed by oxidation to the same keto-sulphone (IX).

Attempts to confirm the position of the hydroxyl group by desulphurisation of (III) and (Va) with Raney nickel resulted in complete reduction to indane; by comparison with the desulphurisation of (XI) and (XIIa) (see below) this at least indicates that the hydroxyl group is relatively labile.

The reaction of trans-*indene bromohydrin with sodium thiophenate*

The action of bromine on olefins in aqueous media to form bromohydrins invariably yields the *trans*-isomer[22,23] and, although *cis*-indene bromohydrin is not well characterised, there is no doubt that the indene bromohydrin, m.p. 130°, is the *trans*-isomer.

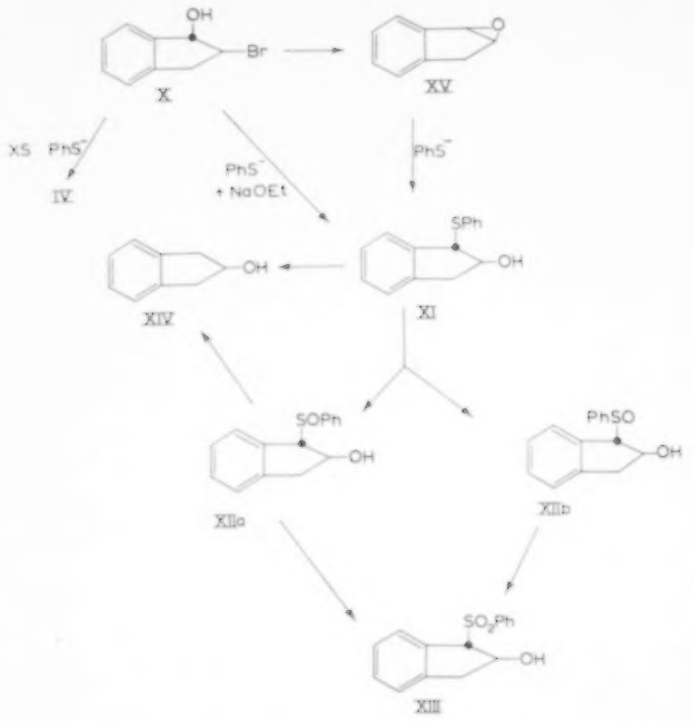
The reaction between indene bromohydrin and sodium thiophenate was found to be sensitive to reaction conditions; data on the quantities of reactants and products formed are collected in Table 1. In Experiments 1 and 3, although the concentrations were 50 per cent higher in the latter, the proportions were identical, with 6 per cent excess of sodium thiophenate and an additional 12 per cent excess of thiophenol. In both cases the products were mixtures; that from Experiment 1 contained (III), as shown by the isolation of (Va) after oxidation, but from Experiment 3, (IV) must have been the major product, because it separated in the solid state and in amount representing one-third of the total product, although it is the lower melting and more soluble isomer. Direct evidence is lacking, but it is probable that (III) and (IV) were present in both products; however, there is no doubt that the yield of (IV) was appreciably higher in Experiment 3 than in Experiment 1.

In Experiment 2, the excess of sodium thiophenate over the bromohydrin was only 1 per cent, but the reaction medium contained sodium ethoxide derived from the 10 per cent excess of sodium. The product was an oil in which small proportions of (III) and (IV) may have been present, but the major constituent and the sulphoxide (XIIa) obtained from it yielded 2-indanol (XIV) on desulphurisation with Raney nickel. The reaction must therefore have involved migration of the hydroxyl group from the 1- to the 2-position and formation of 1-phenylmercapto-2-indanol (XI).

Kinetic evidence regarding the mechanism of the reaction between *trans*-indene bromohydrin and the thiophenate ion is not available, but it is probable that the reaction lies on the borderline between unimolecular (S_N1) and bimolecular (S_N2), because it is sensitive to reaction conditions.[24,25]

In the presence of sodium ethoxide, ionisation of the hydroxyl group will develop a negative charge on the oxygen; this will promote ionisation at the reaction site and accelerate the S_N1 reaction. In addition, the adjacent $-O^-$ group has a strong tendency to participate in the intermediate step[26] and in the present system this would be expected to lead promptly to the formation of epoxide. As shown by direct

[22] P. D. Bartlett, *J. Amer. Chem. Soc.* **57**, 225 (1935).
[23] P. D. Bartlett and R. V. White, *J. Amer. Chem. Soc.* **56**, 2785 (1934).
[24] E. D. Hughes and C. K. Ingold, *J. Chem. Soc.* 244 (1935).
[25] E. D. Hughes, *Trans. Faraday Soc.* **37**, 603 (1941).
[26] S. Winstein, *et al.*, *J. Amer. Chem. Soc.* **70**, 816, 821, 828 (1948).



experiment, attack by thiophenate ion on the epoxide (XV) yields as major product the same compound, (XI), obtained in Experiment 2.

With regard to the stereochemical configuration of the rearranged product, it is known[27,28,29,30] that inversion invariably accompanies epoxide formation and also epoxide ring opening so that retention of the *trans*-configuration is expected for the overall reaction. For this reason, the hydroxysulphoxides (XIIa) and (XIIb) and the hydroxysulphone (XIII) are assigned the *trans*-1-substituted-2-indanol structures.

In alcoholic solution, with a small excess of thiophenol, the hydroxyl group will not be ionised; its participation in the transition state and promoting effect on the S_N1 mechanism will be considerably reduced. This condition prevailed in Experiments 1 and 3 and a 50 per cent increase in concentration of the reactants increased the proportion of (IV) in the product. This may be interpreted either as an increased contribution from the bimolecular (S_N2) mechanism or, alternatively, as a result of a shortening of the life of the cation in the S_N1 reaction with consequent increase in the shielding effect of the receding bromide ion. Either interpretation leads to the conclusion that the isomer (IV) favoured by increased concentration is the *cis* form.

If the above interpretations are correct, it should be possible by reducing the dielectric constant of the medium and increasing the thiophenate-ion concentration to inhibit the S_N1 mechanism and promote the S_N2. Experiment 4 was therefore

[27] D. Swern, *J. Amer. Chem. Soc.* **70**, 1235 (1948).
[28] D. Swern, *Organic Reactions* (Ed.-in-Chief Roger Adams) Vol. VII, p. 387. Wiley, New York (1953).
[29] F. G. Bordwell and R. J. Kern, *J. Amer. Chem. Soc.* **77**, 1141, (1955).
[30] S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.* **61**, 1581 (1939).

carried out with a fourfold excess of thiophenate ion and, as solvent, thiophenol containing the minimum amount of ethanol necessary to dissolve the thiophenate. An 89 per cent recovery of product was achieved and it was virtually pure hydroxysulphide (IV). This provides convincing confirmation of the assignments of configuration made on the evidence of yields of isomers from the lithium aluminium hydride reduction of (II), namely, that (III), m.p. 102°, is *trans* and (IV), m.p. 72°, is *cis*.

EXPERIMENTAL*

Infra-red absorption spectra† were recorded for all the substances described. The method of Barnard and Hargrave[31] used for estimation of hydroperoxide and sulphoxide was modified only by the addition of acetic acid (10 ml) at the same time as the titanous chloride and ammonium thiocyanate, to ensure solubility of the sulphoxides in the aqueous media.

Co-oxidation of indene and thiophenol. Indene (obtained from Gesellschaft für Teerverwertung, Duisberg-Meiderich) was distilled under nitrogen (oxygen content not greater than 0·001 per cent), b.p. 67°/13 mm, n_D^{20} 1·5765, f.p. —1·549°, purity determined by freezing point[32] was not less than 99·5 per cent. Thiophenol was also distilled under nitrogen before use, b.p. 69°/13 mm, n_D^{20} 1·5899.

A solution of indene (0·046 mole) and thiophenol (0·045 mole) in benzene (150 ml) was shaken in an atmosphere of oxygen at 20 ± 0·1° and 760 ± 5 mm. Absorption of oxygen (0·043 mole) was complete in 85 min and mercaptan was not detectable in the product. Immediately after the oxidation 77 per cent of the absorbed oxygen was present as hydroperoxide and 7 per cent as sulphoxide. On subsequent standing, the hydroperoxide decayed by a second-order law and after 140 hr at 20° the hydroperoxide concentration was virtually zero; concurrently, the sulphoxide concentration rose to a value corresponding to 45 per cent of the absorbed oxygen.

Lithium aluminium hydride reduction of the primary co-oxidation products. Isolation of the hydroperoxide was impracticable owing to the ease with which it decomposed.

The reaction mixture at the end of an oxidation similar to that described above was cooled rapidly to 5°, shaken with anhydrous magnesium sulphate, filtered and added slowly to an ice-cooled suspension of lithium aluminium hydride (4 g) in tetrahydrofuran (150 ml). Hydroperoxide in the solution of co-oxidation products was estimated half-way through the addition by titration of a 2 ml sample (Found: —OOH, 0·029 mole in 150 ml; 69 per cent of the oxygen uptake). The reduction reaction mixture was refluxed for 6 hr, after which time water and sodium hydroxide were added; extraction with benzene yielded, on removal of solvent, 9·05 g of brown solid. Chromatography on a silica-gel column gave *trans*-2-phenylmercapto-1-indanol (III) (7·19 g, 0·030 mole), identical in infra-red spectrum and m.p. with synthetic material.

Secondary co-oxidation products. Three separate co-oxidations of indene (5·353 g) and thiophenol (4·95 g) in benzene (300 ml) were carried out at 20° (oxygen absorbed: 1·347 g in each), and the combined reaction mixtures were maintained at 20° until decay of the hydroperoxide was complete. In the later stages of the reaction colourless crystals (8·0 g), m.p. 140–145°, were deposited. After 140 hr the supernatant liquid

* All melting points were corrected. Elementary micro-analyses were carried out by Dr. Ing A. Schoeller of Kronach/Oberfranken, Bambergerstrasse 20, Germany.

† We are indebted to N. G. McTaggart and W. L. Mead for spectroscopic data.

[31] D. Barnard and K. R. Hargrave, *Anal. Chim. Acta* **6**, 23 (1952).

[32] A. R. Glasgow, A. J. Streiff and F. D. Rossini, *J. Res. Nat. Bur. Stand.* **35**, 355 (1945).

(solution *A*) was decanted and the deposits, on recrystallisation from benzene, yielded a pure hydroxysulphoxide, m.p. 150° (Found: —OH, 6·50; =SO, 18·20. Calc. for $C_{15}H_{14}O_2S$: —OH, 6·59; =SO, 18·58 per cent), which was identical in m.p. and infra-red spectrum with the synthetic high-melting isomer of *trans*-2-phenylsulphinyl-1-indanol (Va) and did not depress its m.p.

Solution *A* was diluted with an equal volume of *n*-pentane and the resulting white precipitate consisting (infra-red spectrum) of a mixture, m.p. 80–125°, of the *trans*-hydroxysulphoxides (Va) and (Vb) (8·3 g)(Found: —OH, 6·40; =SO, 18·40 per cent), was filtered off.

The benzene–pentane filtrate, after removal of solvent under reduced pressure, left a brown viscous oil, from which a small amount of indene (1·3 g; n_D^{20} 1·5768) was recovered by distillation in high vacuum. On trituration of the residue with carbon tetrachloride crystals separated (8·3 g), consisting of the low-melting *trans*-2-phenylsulphinyl-1-indanol (Vb), which after crystallisation from benzene–*cyclo*hexane melted at 99° (Found: —OH, 6·26; =SO, 18·20. Calc. for $C_{15}H_{14}O_2S$: —OH, 6·59; =SO, 18·58 per cent). This material was identical in m.p. and infra-red spectrum with synthetic (Vb) and did not depress its m.p.

Removal of carbon tetrachloride from the remaining solution yielded a viscous oil (8·76 g), which was adsorbed on a column of silica gel and eluted by solvents of increasing polarity. The first two components were diphenyl disulphide (0·6 g; m.p. and mixed m.p. with authentic material, 61°) and *trans*-2-phenylmercapto-1-indanol (III) (0·65 g), identified by infra-red spectrum, m.p. and mixed m.p., 102°. Further quantities of (Va) (1·50 g, m.p. 150)°, were also isolated; other fractions (1·4 g) had spectra closely resembling those of (Va) and (Vb).

The hydroxysulphoxides and hydroxysulphide together accounted for 86 per cent of the oxygen absorbed during co-oxidation. The remaining fractions were not identified, but infra-red spectra indicated the presence of various sulphides, ketones, ketosulphides and ketosulphoxides. One fraction (0·09 g) exhibited an infra-red spectrum approximating closely to those of the *cis*-2-phenylsulphinyl-1-indanols.

Oxidation of the hydroxysulphoxides from co-oxidation. The substances (Va), m.p. 150°, (Vb), m.p. 99°, and the mixture, m.p. 80–125°, separated from the co-oxidation products after decay of peroxide were oxidised in acetic acid solution with a five-fold excess of 30 per cent hydrogen peroxide. All three samples gave theoretical yields of *trans*-2-phenylsulphonyl-1-indanol (VII), identical in their infra-red spectra and showing undepressed m.p. with synthetic material.

A mixture containing 95 per cent by weight of (VII) and 5 per cent by weight of the *cis* isomer (VIII) began to liquefy at 105° and completely melted at 115°; the crude hydroxysulphone obtained from the mixture m.p. 80–125° melted at 115–117·5°. It is therefore probable that, if the mixture of hydroxy-sulphoxides contained any *cis*-isomers, the proportion was considerably less than 5 per cent.

trans-*Indene bromohydrin* (X). Indene bromohydrin, m.p. 130°, was prepared by the method of Pope and Read.[33]

2-*Bromo*-1-*indanone* (I). A modification of Courtot's method [18] in which chromic acid in acetic acid was employed to oxidise the bromohydrin (0·4 mole) gave a 61 per cent yield of bromoketone, m.p. 33·5–34·5° (Courtot: 38°).

2-*Phenylmercapto*-1-*indanone* (II). The bromoketone (0·2 mole) dissolved in dry

[33] W. J. Pope and J. Read, *J. Chem. Soc.* **101**, 758 (1928).

methanol (200 ml) was slowly added, in an atmosphere of nitrogen, to a solution of sodium thiophenate prepared from sodium (5 g), dry methanol (150 ml) and thiophenol (0·196 mole). After 15 min under reflux, 175 ml of methanol was distilled off and refluxing was continued for 1 hr; the reaction mixture was then poured into water (1 l.) and extracted with several portions of benzene. The combined extracts were washed with 5% sodium hydroxide and water and dried over anhydrous magnesium sulphate. Removal of solvent left a solid residue, which yielded, after repeated crystallisation from *cyclo*hexane, 48·4 g (63 per cent) of a slightly impure product, m.p. 65–67·5°. Recrystallisation from benzene–*cyclo*hexane gave pure 2-*phenylmercapto*-1 *indanone* (II) m.p. 66–67° (Found: C, 74·90; H, 5·20; S, 13·57. Calc. for $C_{15}H_{12}OS$: C, 74·99; H, 5·04; S, 13·31 per cent); *semicarbazone*, m.p. 188° (Found: C, 64·65; H, 4·98; N, 14·31; S, 11·07. Calc. for $C_{16}H_{15}ON_3S$: C, 64·63; H, 5·09; N, 14·14; S, 10·76 per cent); 2:4-*dinitrophenylhydrazone*, m.p. 191° (Found: C, 60·07; H, 3·75; N, 13·17; S, 7·82. Calc. for $C_{21}H_{16}O_4N_4S$: C, 59·99; H, 3·84; N, 13·33; S, 7·61 per cent). The ketosulphide regenerated from the semicarbazone was unchanged in m.p.

trans- *and* cis-2-*Phenylmercapto*-1-*indanol* [(III) *and* (IV)]. A solution of 2-phenylmercapto-1-indanone (4·2 g) in sodium-dried ether (30 ml) was slowly added with stirring to a slurry of lithium aluminium hydride (1 g) in dry ether (50 ml) and refluxed for 3 hr. The product (4·08 g, 96 per cent) was isolated in the usual way.[34] Fractional crystallisation from *cyclo*hexane–pentane mixtures yielded the two isomers: trans-2-*phenylmercapto*-1-*indanol* (III), m.p. 102° (2.7 g, 64 per cent). (Found: C, 74·05; H, 5·90; S, 13·38; —OH, 7.2. Calc. for $C_{15}H_{14}OS$: C, 74·37; H, 5·82; S, 13·20; —OH, 7·05 per cent); *phenylurethane*, m.p. 121° (Found: C, 73·19; H, 5·39; N, 4·10; S, 8·85. Calc. for $C_{22}H_{19}O_2NS$: C, 73·10; H, 5·28; N, 3·87; S, 8·87 per cent); and cis-2-*phenylmercapto*-1-*indanol* (IV) m.p. 72° (0·6 g, 14 per cent) (Found: C, 74·49; H, 5·97; S, 13·43; —OH, 7·0 per cent); *phenylurethane*, m.p. 124° (Found: C, 72·91; H, 5·30; N, 4·17; S, 8·80 per cent). The infra-red spectra of the two isomers were much alike, but differed in detail. A mixed m.p. of the phenylurethanes was depressed to 97–105°. Desulphurisation of (III) with Raney nickel yielded indane, identified by refractive index (n_D^{20} 1·5380) and by its retention volume on a gas-chromatography column.

Attempted isomerisation of the trans- *and* cis-2-*phenylmercapto*-1-*indanols*. *cis*-2-Phenylmercapto-1-indanol (IV) (0·12 g) was heated with lithium aluminium hydride (0·05 g) in sodium-dried ether (7 ml) for 4 hr. After working up in the usual manner, the starting material was recovered (0·11 g), m.p. 70–71°, but with a faint odour of thiophenol.

The hydroxysulphide (IV) (0·5 g) was refluxed under nitrogen for 4 hr with 10% alcoholic potassium hydroxide (5 ml). After neutralisation with carbon dioxide, filtration and evaporation, the starting material was again recovered (0·45 g), m.p. 70·5–72°.

trans-2-Phenylmercapto-1-indanol (III) (0·2 g) was refluxed with 10% alcoholic potassium hydroxide (2 ml) for 8 hr. After neutralisation with carbon dioxide and filtration, the brown solution was decolorised with charcoal and evaporated. The infra-red spectrum of the product (0·12 g), m.p. 80–90°, indicated that about 50 per cent had decomposed to an unidentified substance other than (IV).

The hydroxysulphide (III) (0·5 g) was heated in an evacuated sealed tube with 10%

[34] R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.* **69**, 1197 (1947).

alcoholic potassium hydroxide at 100° for 4 hr. After working up with carbon dioxide, the starting material was recovered unchanged, m.p. 101–102°.

trans-2-*Phenylsulphinyl*-1-*indanols* [(Va) *and* (Vb)]. The hydroxysulphide (III) (1·15 g) was oxidised in acetic acid solution with a 10 per cent excess of 30% hydrogen peroxide, the solution being cooled to 5° during addition of the reagent and then allowed to stand at room temperature for 24 hr. By fractional crystallisation of the product (1·23 g, 100 per cent) from benzene–*cyclo*hexane, *the two* trans-2-*phenylsulphinyl*-1-*indanols* were isolated: (Va) (0·31 g), m.p. 149·5–150·5° (Found: C, 69·94; H, 5·65; S, 12·40; =SO, 18·20; —OH, 6·39, 6·50) and (Vb) (0·25 g), m.p. 99° (Found: C, 69·66; H, 5·40; S, 12·40; =SO, 18·20; —OH, 6·26. Calc. for $C_{15}H_{14}O_2S$: C, 69·77; H, 5·46; S, 12·39; =SO, 18·58; —OH, 6·59 per cent). The spectra of the high- and low-melting isomers were similar, but differed in detail. From the m.p. and quantities of the intermediate fractions, it was estimated that the two isomers were formed in equal proportions. Desulphurisation of (Va) with Raney nickel yielded indane.

cis-2-*Phenylsulphinyl*-1-*indanols* [(VIa) *and* (VIb)]. Oxidation of the hydroxysulphide (IV) (2·6 g) by the method used for the *trans* isomer gave a colourless gum (2·3 g) from which were separated *the two* cis-2-*phenylsulphinyl*-1-*indanols*: (VIa) (0·9 g), m.p. 158° (Found: C, 69·36; H, 5·52; S, 12·68) and (VIb, (0·9 g) m.p. 122–123° (Found: C, 69·84; H, 5·61; S, 12·90. Calc. for $C_{15}H_{14}O_2S$: C, 69·77: H, 5·46; S, 12·39 per cent). The infra-red spectra of these two isomers were similar, but differed considerably from those of the isomers (Va) and (Vb).

trans-2-*Phenylsulphonyl*-1-*indanol* (VII). The hydroxysulphide (III) (0·75 g), oxidised in chloroform solution by shaking with acid permanganate solution and working up in the usual manner,[35] yielded trans-2-*phenylsulphonyl*-1-*indanol* (VII) (0·3 g), m.p. 122° (Found: C, 65·55; H, 5·17; S, 11·72. Calc. for $C_{15}H_{14}O_3S$: C, 65·69; H, 5·14; S, 11·66 per cent). The infra-red spectrum showed characteristic hydroxyl and sulphone bands.

cis-2-*Phenylsulphonyl*-1-*indanol* (VIII). Oxidation of (IV), (VIa) and (VIb) in acetic acid solution with five-fold excess of 30% hydrogen peroxide and crystallisation of the products from benzene–*cyclo*hexane gave 95 per cent yields of cis-2-*phenylsulphonyl*-1-*indanol* (VIII), m.p. 131° (Found: C, 65·76; H, 5·24; S, 11·68. Calc. for $C_{15}H_{14}O_3S$: C, 65·69; H, 5·14; S, 11·66 per cent). Mixed m.p. of the three preparations showed no depression.

2-*Phenylsulphonyl*-1-*indanone* (IX). Oxidation of (III), (VII) and (VIII) (2 millimoles) in acetic acid solution with chromic acid (4 millimoles) at 40° (20 min) and permanganate oxidations of (II) and (IV) yielded in all cases 2-*phenylsulphonyl*-1-*indanone* (IX), m.p. 147–148°. The infra-red spectrum of the product from (VII) was consistent with a pure ketosulphone structure (Found: C, 66·23; H, 4·67; S, 12·52. Calc. for $C_{15}H_{12}O_3S$: C, 66·16; H, 4·44; S, 11·77 per cent). *The* 2:4-*dinitro-phenylhydrazone* formed yellow needles from ethyl acetate, m.p. 262° (Found: C, 55·63; H, 3·68; N, 12·38; S, 7·12. Calc. for $C_{21}H_{16}O_6N_4S$: C, 55·74; H, 3·56; N, 12·38; S, 7·08 per cent).

The reaction of trans-*indene bromohydrin with sodium thiophenate*. Four experiments were carried out under different conditions as shown in Table 1; in each an atmosphere of nitrogen was maintained over the reaction mixture. Sodium thiophenate was

[35] J. L. Cunneen, *J. Chem. Soc.* 36 (1947).

TABLE 1. THE REACTION OF *trans*-INDENE BROMOHYDRIN WITH SODIUM THIOPHENATE

Experiment	1	2	3	4
Bromohydrin solution:				
Indene bromohydrin (mole)	0·047	0·665	0·094	0·05
Ethanol (ml)	65	250	110	5
Benzene (ml)	—	200	—	—
Thiophenol (ml)	—	—	—	70
Thiophenate solution:				
Sodium (g-atom)	0·050	0·740	0·100	0·25
Thiophenol (mole)	0·056	0·673	0·112	0·5(50 ml)
Ethanol (ml)	70	350	100	35
Reaction temperature (°C)	Reflux	Reflux	Reflux	50–60
Time of reaction (min)	30	10	45	120
Product:	Oil	Oil		Solid
Yield (per cent of theoretical)	82	71	28 (solid*) 57 (oil)	87 (IV, <2 (other material)
$n_D^{\dagger}$	1·6359	1·6368	—†	
Phenylurethane, m.p. (°C)	—	147	124	124
Derived sulphoxides	(Va) (25%)	(XIIa), (XIIb) (44% of each)	(VIa), (VIb) (50% of each)	

* (IV)
† Dehydration occurred during distillation of the oil and it was not investigated further.

prepared by dissolving clean sodium in ethanol containing thiophenol and a solution of the bromohydrin was added slowly with stirring. After a period for reaction, the bulk of the solvent was removed at low pressure and the residue was taken up in ether or benzene and 5–7% aqueous sodium hydroxide. Excess of thiophenol was removed from the organic layer by extraction with alkali, followed by water washing and drying over anhydrous magnesium sulphate; the solvent was finally removed under reduced pressure. The liquid products from Experiments 1 and 2 were distilled in vacuum; the solid products from Experiments 3 and 4 were crystallised from *cyclo*hexane–pentane. Phenylurethanes and sulphoxides were prepared from the various products by the usual methods.

Investigation of the product from Experiment 2. The product from Experiment 2 was a viscous orange oil, n_D^{20} 1·6368 (Found: —OH, 6·9. Calc. for $C_{15}H_{14}OS$: —OH, 7·05 per cent), with an infra-red spectrum showing bands characteristic of hydroxyl and sulphide but no other oxygen- or sulphur-containing groups. A phenylurethane was obtained in good yield, m.p. 146–147°, not depressed on admixture with the phenylurethane of the product obtained by the action of sodium thiophenate on indene epoxide (see below).

The hydroxysulphide oil (2·14 g) dissolved in ethanol (150 ml) was refluxed for 2 hr with Raney nickel (40 g). After filtration, the bulk of the solvent was removed by distillation through a 35 cm column packed with Fenske helices. The residue yielded

0·55 g (50 per cent of theoretical) of 2-indanol, m.p. 68–69°, phenylurethane, m.p. 131·5–132·5°.

The product from Experiment 2 must therefore be a mixture of isomeric hydroxysulphides, the major component of which is *trans*-1-phenylmercapto-2-indanol (XI).

trans-1-*Phenylsulphinyl*-2-*indanols* [(XIIa) *and* (XIIb)]. Oxidation of the product from Experiment 2 (10 g) in acetic acid solution with 10 per cent excess of 30% hydrogen peroxide gave a pale-yellow viscous oil (10 g). Trituration with benzene separated a solid (4·6 g), m.p. 145–148°, which on recrystallisation from benzene yielded the *high-melting isomer* of trans-1-*phenylsulphinl*-2-*indanol* (XIIa), m.p. 157–158° (Found: C, 70·03; H, 5·39; S, 12·13; —OH, 5·9; =SO, 18·0. Calc. for $C_{15}H_{14}O_2S$: C, 69·77; H, 5·46; S, 12·39; —OH, 6·59; =SO, 18·58 per cent). The mixed m.p. with the hydroxysulphoxide (VIa), m.p. 158°, was depressed to 110–120°.

Evaporation of the mother-liquors left a solid (4·0 g), m.p. 125–129°, which yielded on crystallisation from *cyclo*hexane–benzene (50:50), the *low-melting isomer of* trans-1-*phenylsulphinyl*-2-*indanol* (XIIb), m.p. 133–134·5° (Found: C, 70·13; H, 5·58; S, 12·51. Calc. for $C_{15}H_{14}O_2S$: C, 69·77; H, 5·46; S, 12·39 per cent). By desulphurisation of the high-melting isomer (0·6 g in 80 ml of ethanol) with Raney nickel as described for the product of Experiment 2, the same 2-indanol, (0·06 g, 20 per cent m.p. 68–69°, and its phenylurethane, m.p. 131–132°, were obtained.

The final mother-liquors contained a solid (0·7 g), m.p. 99–110°, raised by crystallisation from benzene-*cyclo*hexane to 113·5–114·5°; mixed m.p. with the hydroxysulphone (XIII) (see next paragraph) was not depressed.

trans-1-*Phenylsulphonyl*-2-*indanol* (XIII). Oxidation of the hydroxysulphoxides (XIIa) and (XIIb) in acetic acid with excess of 30% hydrogen peroxide gave theoretical yields of trans-1-*phenylsulphonyl*-2-*indanol* (XIII); the m.p. of the two samples and their mixed m.p. were 114–115° (Found: C, 65·72; H, 4·92; S, 11·86. Calc. for $C_{15}H_{14}O_3S$: C, 65·69; H, 5·14; S, 11·66 per cent). A mixed m.p. with the hydroxysulphone, m.p 122°, was depressed to 97–110°.

trans-1-*Phenylmercapto*-2-*indanol* (XI). Indene epoxide (0·35 mole), prepared by the method of Boeseken[35] was treated with sodium thiophenate (0·36 mole) in 50% aqueous ethanol, following the procedure of Bordwell and Kern.[29] The product (9·05 g) was a pale-yellow viscous oil, n_D^{20} 1·6294 (Found: —OH, 6·0 Calc. for $C_{15}H_{14}OS$: —OH, 7·05 per cent). Although the product was evidently impure owing to partial dehydration, the *phenylurethane* of trans-1-*phenylmercapto*-2-*indanol* was obtained in 70 per cent yield, m.p. 143–146°, raised by crystallisation from *cyclo*hexane to 146–147° (Found: C, 72·90; H, 5·30; N, 4·28; S,8·67. Calc. for $C_{22}H_{19}O_2NS$: C, 73·10; H, 5·28; N, 3·87; S, 8·87 per cent).

Acknowledgement—We thank the Chairman and Directors of the British Petroleum Company for permission to publish this work.

[35] J. Boeseken and C. van Loon, *Proc. Kon. Akad. Wet., Amst.* **20**, 1186 (1918); *Chem. Abstr.* **13**, 314 (1919).

Tetrahedron, 1958, Vol. 4, pp. 337–341. Pergamon Press Ltd., London

THE DIPOLE MOMENTS AND THE STRUCTURES OF CHLORO- AND BROMO-CROTONOLACTONES

KUNIO SUKIGARA, YOSHITERU HATA,* YUKIO KURITA and MASAJI KUBO
Chemical Department, Nagoya University, Chikusa, Nagoya, Japan

(*Received* 2 *June* 1958)

Abstract—The dipole moments of the isomeric pairs of bromocrotonolactones and of chlorocrotonolactones were measured in benzene solutions at 25° along with those of butyrolactone and crotonolactone. Based on the observed moments of the last two compounds, theoretical calculations were made of the moments of these halocrotonolactones for both α- and β-modifications. The comparison between the observed and calculated moments showed definitely that, of the isomeric pair of bromocrotonolactones, one having a greater moment 4·70 D and a lower melting point 57° is the α-modification and the other isomer having a moment of 3·86 D and a melting point of 77° is the β-modification. Similarly, α-chlorocrotonolactone shows a moment of 4·83 D and melts at 27° while the corresponding β-modification has a moment of 3·57 D and a melting point of 51–52·5°. The result is in good agreement with the conclusion derived from the infra-red absorptions of these compounds and affords an unequivocal evidence in favour of the correctness of the reasoning advanced by Gilman *et al.*, by Whiting, and by Owen and Sultanbawa against the presumption of Hill and his followers. Thus, the long pending problem on the constitutional formulae of isomeric α- and β-halocrotonolactones has been settled.

INTRODUCTION

THE problem on the constitutional formulae of isomeric α- and β-halocrotonolactones has been a subject of considerable dispute. Hill and Cornelison[1] reduced 3:4-dibromocrotonolactone with zinc and acetic acid and obtained bromocrotonolactone of m.p. 58°. The same compound was obtained, when they treated 3:5-dibromo-2-furoic acid with hydrogen bromide. On the other hand, both the treatment of 3-bromo-2-furoic acid with bromine water and that of 3:5-dibromo-2-furoic acid with bromine gave an isomeric bromocrotonolactone of m.p. 77°. From these methods of synthesis, the former was presumed to be 4-bromocrotonolactone or the β-modification, while the latter a 3-bromo-compound or the α-modification. Similar synthesis was also carried out for chlorocrotonolactones. Thus, 3:4-dichlorocrotonolactone and 3:5-dichloro-2-furoic acid gave chlorocrotonolactone of m.p. 25–26°, when they were treated with zinc and acetic acid and with sulphuric acid, respectively. An isomeric chlorocrotonolactone of m.p. 52–53° was obtained, when 3:5- and 4:5-dichloro-2-furoic acids were subjected to reaction with bromine and hydrogen bromide, respectively. The former product was assigned the structure of the β-modification and the latter that of the α-modification. These authors prepared various derivatives of this type and determined their structures on the basis of this

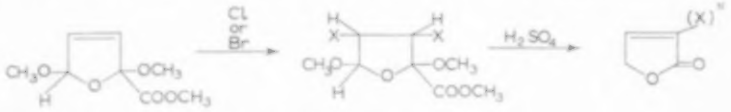
* Institute of Scientific and Industrial Research, Osaka University, Sakai-shi, Japan.
[1] H. B. Hill and R. W. Cornelison, *Amer. Chem. J.* **16**, 188 (1894).
[2] R. Lespieau and P. L. Viguier, *C.R. Acad. Sci., Paris* **148**, 491 (1909).

conclusion. Later, Lespieau and Viguier[2] prepared a compound identical with the α-modification of Hill and Cornelison by the following reaction.

Thus, a choice was made between the alternatives of the addition of hydrogen bromide on the triple-bonded carbon atoms simply in accordance with the Hill and Cornelison's presumption.

Meanwhile, Gilman *et al.*[3] pointed out that the structures of substituted 2-furoic acids employed by Hill and his co-worker were in error. Whiting[4] also argued against the simple reasoning of Lespieau and Viguier by calling attention to the general rule that halogen takes the β-position rather than the α-position as they presumed in explaining the reaction that they had carried out. His argument is nothing more or less than the denial of the Hill's original presumption. In the same year, Owen and Sultanbawa[5] prepared bromocrotonolactone of m.p. 59–60° (β-modification according to Hill *et al.*) from α,β,γ-tribromobutyric acid. Taking account of the fact that the bromine atom at the α-position was the most firmly bound one among the three bromine atoms, they maintained that they obtained α-bromocrotonolactone. In this prolonged controversy, it was difficult to arrive at a conclusion, because no arguments carried conviction.

Murakami and Hata[6] have pursued the addition reactions of halogen to methyl 2:5-dimethoxy-2:5-dihydro-2-furoate at its 3:4-positions as well as the ring opening reactions of the resulting addition products. It was found that when dihalo compounds were heated with 50% sulphuric acid they did not suffer a loss of hydrogen halide followed by ring opening as expected, but gave halocrotonolactones (m.p. of bromo- and chloro-compounds, 57° and 27°, respectively) besides some by-products.



[9] (X) signifies that the position of X is not yet clear at this stage.

Accordingly, the settlement of the aforementioned question of long standing became an urgent problem. Therefore, for both bromo- and chlorocrotonolactones thus obtained, the isomeric compounds (m.p. of bromo- and chloro-compounds, 77° and 51–52·5° respectively) were prepared by the method of Lespieau and Viguier and their infra-red absorptions were recorded.[6] It was found that the frequency of the C=O band at about 1750 cm^{-1} of the isomer having the lower melting point was higher by 17 cm^{-1} than that of the isomeric partner of the bromo derivatives and the corresponding wave number shift was 25 cm^{-1} for the chloro derivatives. The blue shift of C=O absorptions due to the presence of halogen at the α-position has been amply exemplified with a number of data on substituted aliphatic ketones, *cyclo*hexanones and steroids.[7] Therefore, the isomers having lower melting points were considered to be α-modifications in contradiction to Hill's presumption.

[2] H. Gilman and G. F. Wright, *Chem. Rev.* **11**, 323 (1932); H. Gilman, R. J. Vander Wal, R. A. Franz and E. V. Brown, *J. Amer. Chem. Soc.* **57**, 1146 (1935).
[4] M. C. Whiting, *J. Amer. Chem. Soc.* **71**, 2946 (1949).
[5] L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.* 3105 (1949).
[6] M. Murakami and Y. Hata, Reported in part at the 11th Annual Meeting of the Chemical Society of Japan, April 1958. To be published.
[7] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952); E. J. Corey, *Ibid.* **75**, 2301, 3297 (1953); L. J. Bellamy and R. L. Williams, *J. Chem. Soc.* 4294 (1957)

The present investigation was undertaken in order to confirm this point by dipole moment measurements. This method was hoped to be capable of settling the pending problem by a more direct physical method of attack. For this purpose, measurements were carried out of the moments of four halocrotonolactones mentioned above and some related compounds.

EXPERIMENTAL

Bromocrotonolactone of m.p. 57° and chlorocrotonolactone of m.p. 27° were prepared by Murakami and Hata's[6] method. Bromocrotonolactone of m.p. 77° and chlorocrotonolactone of m.p. 51–52·5° were synthesised by a method due to Lespieau and Viguier.[2] The synthesis of crotonolactone was carried out after Glattfeld *et al.*,[8] b.p. being 71–72°/7 mm. Commercial butyrolactone was fractionated by means of a Stedman packing column and a fraction boiling at 67·5°/8 mm was taken.

The measurements were carried out at 25° on dilute solutions in benzene. The dielectric constants were measured by means of a heterodyne beat apparatus provided with a platinum cell.[9] For each solute, the determinations of the dielectric constant and density were made on solutions of four different concentrations appropriately chosen below about 0·7 per cent. The graphical plots of the dielectric constant as well as the density of solutions against the concentration in weight per cent gave linear dependence within experimental errors. From the slopes of these straight lines, the molar polarisations of the solutes were calculated by a method similar to that introduced by Halverstadt and Kumler,[10] differing in that densities were used rather than the specific volumes. The sum of electronic and atomic polarisations of each of these compounds was approximated with the molar refraction for the D-line calculated from bond refractions.[11] In order to check the adequacy of this procedure, the refractive indices and densities of butyrolactone and crotonolactone were measured to evaluate $P_E + P_A$. The values were 20·06 and 19·28 cm³, respectively, in good agreement with 20·34 and 20·87 cm³ calculated from bond refractions.

TABLE 1. DIPOLE MOMENTS OF HALOCROTONOLACTONES AND RELATED COMPOUNDS IN BENZENE SOLUTIONS AT 25°. $\varepsilon_1 = 2{\cdot}2709$, $d_1 = 0{\cdot}8722$.

Lactones	m.p.	α	β, (g/cm³)	P_∞ (cm³)	MR_D, (cm³)	μ (D)
Butyro-		21·85	0·192	377·0	20·34	4·13
Crotono-		27·48	0·226	457·6	20·87	4·62
Br-crotono-	57°	15·31	0·749	477·2	27·58	4·70
Br-crotono-	77°	10·06	0·519	331·8	27·58	3·86
Cl-crotono-	27°	21·19	0·239	502·2	24·70	4·83
Cl-crotono-	51–52·5°	12·83	0·804	285·3	24·70	3·57

[8] J. W. E. Glattfeld, G. Leavell, G. E. Spieth and D. Hutton, *J. Amer. Chem. Soc.* **53**, 3164 (1931).
[9] Y. Kurita and M. Kubo, *J. Amer. Chem. Soc.* **79**, 5460 (1957); B. Eda, K. Tsuda and M. Kubo, *Ibid* **80**, 2426 (1958).
[10] I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.* **64**, 2988 (1942).
[11] A. I. Vogel, W. T. Cresswell, G. H. Jeffery and J. Leicester, *J. Chem. Soc.* 514 (1952).

The results are shown in Table 1, in which ε_1 and d_1 denote, respectively, the dielectric constant and density of the solvent; α and β are, respectively, the changes of the dielectric constant and density of the solutions with the weight fraction of the solute; other notations have their usual significances.

DISCUSSION

The only data found in the literature for the moments of these compounds is that of butyrolactone 4·12 D (Marsden and Sutton[12]) in good agreement with 4·13 D of the present investigation.

In order to calculate the theoretical moments for the α- and β-modifications of halocrotonolactones, it is necessary to find the direction of the moment of crotonolactone in the molecule. This was done in the following way. For the sake of simplicity, let it be assumed that five-membered heterocyclic rings take the regular pentagon form. To the first approximation, the moment of butyrolactone may be approximated with the vector sum of the moment of *cyclo*pentanone 2·86 D[13] and that of tetrahydrofuran 1·68–1·71 D.[14] The vector sum of 3·76 D does not perfectly agree with the observed value of 4·13 D. To the second approximation, an additional moment (0·56 D in its magnitude) due to the partial migration of the lone pair electrons of the ring oxygen to the carbonyl oxygen was taken into account in such a way that the resultant moment agrees with the observed value. From these three component moments of known magnitudes and directions, the direction of moment of a butyrolactone molecule could be determined. It points along a direction making an angle of about 19°20′ with the C=O direction on the side of the ring oxygen.

A small increase of the moment of crotonolactone over that of butyrolactone can be presumed to have its origin mainly in the partial migration of π-electrons of a C=C double bond in the heterocyclic ring to the carbonyl oxygen. The resulting moment due to this partial migration can be treated by means of the concept of mesomeric moment due to Sutton *et al.*[15] According to their empirical data, the presence of a carbonyl oxygen in this conjugation system induces mesomeric moments of 0·3 D and 0·1 D in the C=C and C—C bonds of C=C—C=O, respectively, with their negative ends pointing to the right. The resultant of the moment of butyrolactone and these mesomeric moments is 4·49 D in fair agreement with the observed value, 4·62 D. It is directed along a line making an angle of 18°50′ with the C=O direction on the side of the ring oxygen.

Now that the magnitude and the direction of the moment of crotonolactone have been determined, it is easy to calculate the moments for the α- and β-modifications of halocrotonolactones. The C—Br and C—Cl moments in the molecules of these compounds are approximated with 1·60 D, since the corresponding moments in aromatic molecules are practically the same for bromo and chloro compounds. The theoretical moments thus calculated are shown in Table 2.

The comparison shows definitely that, of the isomeric pair of bromocrotonolactones, one having a greater moment and a lower melting point is the α-modification

[12] R. J. B. Marsden and L. E. Sutton, *J. Chem. Soc.* 1383 (1936).
[13] Hs. H. Günthard and T. Gäumann, *Helv. Chim. Acta* **34**, 39 (1951).
[14] L. G. Wesson, *Tables of Electric Dipole Moments*. The Technology Press, Cambridge, Mass. (1948).
[15] J. B. Bentley, K. B. Everard, R. J. B. Marsden and L. E. Sutton, *J. Chem. Soc.* 2957 (1949).

and the other isomer is the β-modification. The same is true for the chlorocrotonolactones. This affords an unequivocal evidence in favour of the correctness of the reasoning advanced by Gilman *et al.*,[3] by Whiting,[4] and by Owen and Sultanbawa[5] against the presumption of Hill[1] and his followers.[2]

TABLE 2. THEORETICAL MOMENTS OF CROTONOLACTONE AND HALOCROTONOLACTONES COMPARED WITH THE OBSERVED ONES

Lactones	$\mu_{theor.}$	$\mu_{obs.}$
Crotonolactone	4·49 D	4·62 D
α-Bromocrotonolactone	4·74	4·70
β-Bromocrotonolactone	3·01	3·86
α-Chlorocrotonolactone	4·74	4·83
β-Chlorocrotonolactone	3·01	3·57

The agreement between the observed and calculated moments is fairly good for the α-modifications, but is not so good for the β-modifications. This was anticipated, because the lone pair electrons of a halogen atom partly migrate into the conjugated double bond system. The resulting change in moment is smaller for the α-modification, because the geometric configuration leads to the partial cancellation of secondary moments due to conjugation effect, whereas in the β-modification they almost co-operate with one another to give a greater net effect.

Acknowledgement—We wish to express our thanks to Prof. M. Murakami of Osaka University for his continued interest in this research.

Tetrahedron, 1958, Vol. 4, pp. 342–350. Pergamon Press Ltd., London

A SYNTHESIS OF LAUDANINE AND (±)-PSEUDOCODAMINE: RESOLUTION INTO THE OPTICAL ISOMERS

BENJAMIN FRYDMAN, RENATE BENDISCH and VENANCIO DEULOFEU
Laboratorios de Investigación, E. R. Squibb and Sons, Argentina S.A.,
Martinez, Pcia. de Buenos Aires, Argentina

(*Received* 4 *June* 1958)

Abstract—By application of the Bischler–Napieralski reaction, and protection of the phenolic hydroxyl group by benzoylation, laudanine and (±)-pseudocodamine were synthesized. The benzoyl bases were resolved easily with tartaric acid. (+)-Pseudocodamine belongs to the same series as (+)-laudanosine.

Laudanine and the laudanidines

LAUDANINE is a racemic phenolic alkaloid isolated from opium by Hesse,[1] who also showed its structural relationship to laudanosine. Späth[2] established that the phenolic hydroxyl was located in carbon 4′ of the benzyl group and assigned to it structure (IV; $R_1 = H$, $R_2 = CH_3$).

This structure was confirmed by the synthesis by Späth and Lang,[3] who employed the Bischler–Napieralski reaction for the formation of the *iso*quinoline ring. Protection of the phenolic hydroxyl group was provided by carbethoxylation. Laudanine was also obtained by demethylation of (±)-laudanosine, as was done by Späth and Burger[4] with hydrochloric acid and by Schöpf and Thierfelder[5] with aluminium chloride.

We report a new synthesis of laudanine by the Bischler–Napieralski reaction, in which the protection of the phenolic hydroxyl group is afforded by benzoylation. The 3′-benzoyloxy-4′-methoxyphenyl-N-2-(3,4-dimethoxyphenyl)ethylacetamide (I; $R_1 = PhCO$, $R_2 = CH_3$) was cyclized under the action of phosphorus pentachloride in cold chloroform solution, and 1-(3′-benzoyloxy-4′-methoxybenzyl)-3,4-dihydro-6,7-dimethoxy*iso*quinoline hydrochloride (II; $R_1 = PhCO$, $R_2 = CH_3$) was obtained in 80 per cent yield. It was transformed into the crystalline methiodide (III; $R_1 = PhCO$, $R_2 = CH_3$), which, when reduced with hydrogen, with platinum oxide as a catalyst, yielded the hydriodide of benzoyllaudanine, from which the crystalline benzoylated base (IV; $R_1 = PhCO$, $R_2 = CH_3$) was prepared. Hydrolysis of the benzoyllaudanine with hydrochloride acid afforded laudanine (IV; $R_1 = H$, $R_2 = CH_3$).

Properties, derivatives and color reactions of the synthetic product were in agreement with those described for natural laudanine. It was transformed into (±)-laudanosine (IV; $R_1 = R_2 = CH_3$) by treatment with diazomethane.

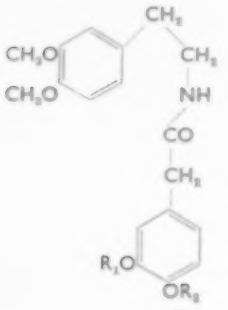
The laevorotatory isomer of laudanine is (−)-laudanidine, an alkaloid which was

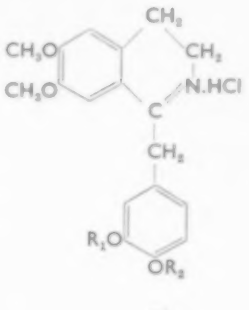
[1] O. Hesse, *Liebigs Ann.* **153**, 47 (1870; *Ber. Dtsch. Chem. Ges.* **4**, 693 (1871)
[2] E. Späth, *Mh. Chem.* **41**, 297 (1920).
[3] E. Späth and N. Lang, *Mh. Chem.* **42**, 273 (1921).
[4] E. Späth and A. Burger, *Mh. Chem.* **47**, 733 (1926).
[5] Cl. Schöpf and K. Thierfelder, *Liebigs Ann.* **537**, 143 (1939).

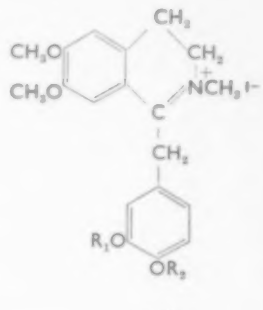
also isolated from opium by Hesse[6] and was shown by Späth and Seka[7] to be identical to the tritopine base of Kauder.[8]

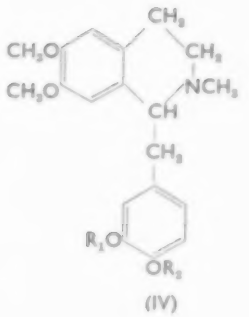
Laudanine [(±)-laudanidine] could not be resolved by Hesse[9] nor by Späth and Burger[4] by employing optical active acids. The stereoisomeric laudanidines were prepared by the latter authors, by treating the optical isomers of laudanosine with hydrochloric acid. (−)-Laudanosine produced the natural (−)-laudanidine.

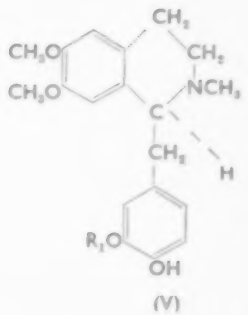
We have found that benzoyllaudanine can be resolved easily by treatment with D-tartaric acid. (+)-Benzoyllaudanidine D-tartrate was obtained, from which the optically active benzoylated base was prepared. Hydrolysis gave (+)-laudanidine. When L-tartaric acid was employed, (−)-laudanidine was obtained. They were identified, by the identity of their physical constants and derivatives, with those described in the literature.


(I)


(II)


(III)


(IV)


(V)

Pseudocodamine

(±)-Pseudocodamine is a racemic phenolic base, which like laudanine and the laudanidines was isolated by Burger[10] from the products formed by the treatment of laudanosine with hydrochloric acid. Burger assigned to it structure (IV; $R_1 = CH_3$, $R_2 = H$), because by ethylation and oxidation 4-ethoxy-3-methoxybenzoic acid was obtained.

[6] O. Hesse, *Liebigs Ann.* **282**, 208 (1894).
[7] E. Späth and R. Seka, *Ber. Dtsch. Chem. Ges.* **58**, 1272 (1925).
[8] E. Kauder, *Arch. Pharm. Berl.* **228**, 419 (1890).
[9] O. Hesse, *J. Prakt. Chem.* [2], **65**, 42 (1902).
[10] A. Bürger, Dissertation, Vienna (1927); A. Bürger, *The Alkaloids* (Ed. R.H.F. Manske and H. L. Holmes) Vol. IV, p. 63. Academic Press, New York (1954).

This structure has been confirmed by a synthesis following similar lines to those described for (±)-laudanine. (±)-Benzoylpseudocodamine (IV; $R_1 = CH_3$, $R_2 = PhCO$) was prepared by identical reactions (I → II → III → IV; $R_1 = CH_3$, $R_2 = PhCO$). The active benzoylpseudocodamines were obtained by resolution of the racemic benzoyl base with D-tartaric and with L-tartaric acid. Acid hydrolysis of the resolved benzoyl bases gave (+)-pseudocodamine and (−)-pseudocodamine. The racemic and the optical active forms of pseudocodamine have the same melting point (130–131°), which does not change when the optical isomers are mixed in different proportions.

(+)-Pseudocodamine was transformed into (+)-laudanosine by treatment with diazomethane. Carbon atom 1 in (+)-pseudocodamine has the structure shown in formula (V). In the nomenclature of Cahn *et al.*,[11] (+)-pseudocodamine is (1 *S*)-1-(4′-hydroxy-3′-methoxybenzyl)-6,7-dimethoxy*iso*quinoline.

EXPERIMENTAL

All the ultraviolet spectra were recorded in 96 per cent ethanol. M.p. are uncorrected.

*Benzoyliso**homovanillic acid.* *iso*Homovanillic acid (10 g) was dissolved in 100 ml of 6 per cent sodium hydroxide solution, 7·0 ml of benzoyl chloride was added and the mixture was shaken well until the odour disappeared. The solution was cooled and acidified with 2 N hydrochloric acid, when an oil, which crystallized easily, was precipitated. The solid was centrifuged, and then washed three times, by centrifugation, with 15 ml of 96 per cent ethanol, to dissolve the benzoic acid formed. It melted at 125–127° and weighed 15·7 g (96 per cent). It could be used without further purification for the preparation of the chloride. For analysis it was recrystallized from ethanol, to give prisms melting at 128°, which were soluble in ether, acetone, chloroform and acetic acid, but less soluble in methanol and benzene (Found: C, 67·94; H, 4·78. Calc. for $C_{16}H_{14}O_5$: C, 67·12; H, 4·95 per cent).

*Benzoyliso**homovanillyl chloride.* Benzoyl*iso*homovanillic acid (10 g) was boiled in a water bath with 50 ml of thionyl chloride for 1 hr. The excess of reagent was removed by distilling under vacuum and the oily residue was kept in a vacuum desiccator over potassium hydroxide. Crystallization of the chloride started very soon and was finished in a few hours. Recrystallized from light petroleum (boiling range 80–90°), 11 g of prisms melting at 86° was obtained; the product was soluble in ether, acetone and chloroform (Found: Cl, 11·11. Calc. for $C_{16}H_{13}ClO_4$: Cl, 11·49 per cent).

3′-Benzoyloxy-4′-methoxyphenyl-N-2-(3,4-*dimethoxyphenyl*)*ethylacetamide* (I; R_1 = PhCO, $R_2 = CH_3$). Benzoyl*iso*homovanillyl chloride (10 g) was dissolved in 40 ml of purified chloroform. The solution was cooled to below 5° and then slowly added to a chloroform solution of 6 g of 3,4-dimethoxyphenylethylamine, also at 5°. The resulting solution was maintained at this temperature for 10 min, and then 25 ml of N sodium hydroxide solution was added to make the aqueous layer alkaline. This was separated by decanting, and the chloroform solution was washed three times with 2 N hydrochloric acid and then with water. After drying, the chloroform was evaporated in vacuum, and the oily residue crystallized in a few hours on standing in

[11] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

a desiccator. Recrystallized from 60 ml of absolute ethanol, 14 g (96 per cent) of the amide was obtained as needles melting at 106°, λ_{max} 276–278 mμ (log ε 3·85), soluble in acetone and chloroform, but less soluble in ether. For analysis it was recrystallized from ethanol and still had m.p. 106° (Found: C, 67·58; H, 5·98; N, 3·07. Calc. for $C_{26}H_{27}NO_6.H_2O$: C, 66·79; H, 6·25; N, 3·00 per cent).

1-(3′-*Benzoyloxy*-4′-*methoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxy*isoquinoline *hydrochloride* (II; R_1 = PhCO, R_2 = CH_3). 3′-Benzoyloxy-4′-methoxyphenyl-N-2-(3,4-dimethoxyphenyl)ethylacetamide (10 g) was dissolved in 100 ml of chloroform, the solution was cooled to 2–3° and 20 g of solid phosphorus pentachloride was slowly added. After the addition was finished, cooling was continued for 3 hr and then the mixture was kept at room temperature (20–25°). A yellow precipitate was formed in the first 24 hr and it did not increase in bulk. After 4 days, 40 g of ice was added, and the chloroform was removed by distilling under vacuum. A brown-yellow solid and water remained in the flask. The water was removed by decantation and the solid was partially dried in a desiccator and then 50 ml of a mixture (1:1) of ethanol and 2 N hydrochloric acid was added. The hydrochloride crystallized very easily as white needles, which after some cooling were filtered off and recrystallized from absolute ethanol (yield 8·2 g; 80 per cent), m.p. 232°. After recrystallization several times from ethanol it had m.p. 233°, λ_{max} 278 mμ (log ε 3·9), 306–307 mμ (3·87) (Found: C, 66·47; H, 5·58; N, 2·83; Cl, 6.95. Calc. for $C_{26}H_{25}NO_5.HCl$: C, 66·72; H, 5·59; N, 2·99; Cl, 7·57 per cent).

1-(3′-*Benzoyloxy*-4′-*methoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxy*isoquinoline *methiodide* (III; R_1 = PhCO, R_2 = CH_3). The hydrochloride (3 g) was suspended in a mixture of 30 ml of water and 30 ml of ethyl ether. A saturated solution of sodium hydrogen carbonate was added to alkalinity, and the free base was extracted with ether. The well dried ether extract was evaporated and the oily residue was boiled with 24 ml of methyl iodide. After a few minutes crystals of the methiodide began to be precipitated. After 30 min the heating was stopped and the excess of methyl iodide was removed by evaporation under vacuum. The orange crystalline solid residue was well dried and recrystallized several times from absolute ethanol to give long yellow needles (yield 3·1 g; 92 per cent), m.p. 224° (Found: C, 54·91; H, 4·51; I, 20·51. Calc. for $C_{26}H_{25}NO_5.CH_3I.H_2O$: C, 54·81; H, 5·05; I, 21·46 per cent).

1-(3′-*Benzoloxy*-4′-*methoxybenzyl*)-6,7-*dimethoxytetrahydro*isoquinoline *hydriodide* (*benzoyllaudanine hydriodide*). The methiodide (2 g) was suspended in 200 ml of absolute ethanol and reduced with hydrogen at 60° and 2 atmospheres, with 400 mg of platinum oxide as catalyst. After 2 hr the methiodide had dissolved. The solution was allowed to cool at room temperature while the reduction was continued for 2 hr more. In some experiments white needles of the hydriodide separated during this last phase of the reaction. They were dissolved by warming the solution, the platinum filtered off and the alcohol was removed by evaporating under vacuum to 50 ml. The crystalline hydriodide was collected after cooling (yield 1·7 g; 85 per cent), m.p. 183°, which did not increase after further crystallizations (Found: C, 56·09; H, 5·26; I, 21·75. Calc. for $C_{27}H_{29}NO_5.HI$: C, 56·38; H, 5·24; I, 22·05 per cent).

Benzoyllaudanine (IV; R_1 = PhCO, R_2 = CH_3). The hydriodide (500 mg) was suspended in a mixture of 10 ml of water and 10 ml of ethyl ether, the suspension was made alkaline with sodium hydrogen carbonate solution, and the base was extracted with ether. By evaporation of the ether extracts, 336 mg of crystalline

benzoyllaudanine (yield 95 per cent), m.p. 154–155°, were obtained. After recrystallization several times from absolute ethanol, it formed prisms, m.p. 156–157°, λ_{max} 284 mμ (log ε 3·87), soluble in cold acetone, chloroform and ether, but less soluble in methanol benzene and dioxan (Found: C, 72·39; H, 6·49; N, 3·15. Calc. for $C_{27}H_{29}NO_5$: C, 72·46; H, 6·53; N, 3·13 per cent).

The crystals gave a reddish color with concentrated nitric acid and a negative reaction with ferric chloride, Millon's reagent and Folin and Ciocalteu's reagent. Benzoyllaudanine does not couple with diazotized *p*-nitroaniline.

Laudanine (IV; $R_1 = H$, $R_2 = CH_3$). To 200 mg of benzoyllaudanine, 20 ml of concentrated hydrochloric acid was added and the suspension was heated to 70° in a water bath, for 45 min. The base dissolved easily and, when the heating was finished, the cooled solution was extracted with ether to remove the benzoic acid. It was then made alkaline with sodium hydrogen carbonate solution and extracted again with ether. The ether extracts were dried and evaporated, when an oily residue was left, which crystallized as soon as a drop of absolute ethanol was added. By filtering, 180 mg of crystals melting 163–164°, with sintering from 159°, were obtained. After several recrystallizations from absolute ethanol, fine needles melting at 164–165° were collected, λ_{max} 284 mμ (log ε 3·78) (Found: N, 4·32. Calc. for $C_{20}H_{25}NO_4$: N, 4·08 per cent). From the product a picrate, obtained as rectangular prisms from ethanol, m.p. 176–177°, and an oxalate, obtained as prisms from water, m.p. 110°, were prepared. Laudanine melts at 163–164°,[5] its picrate 176·5–177·5°[3] and the oxalate 110°.[12]

Synthetic laudanine gives a green-blue color with ferric chloride, a reddish one with nitric acid and with concentrated sulfuric acid, and a blue color with Folin and Ciocalteu's reagent. Millon's reaction is negative. It couples with diazotized *p*-nitroaniline.

(±)-*Laudanosine* (IV; $R_1 = R_2 = CH_3$). Methylation of the synthetic laudanine, in ether solution, with diazomethane gave (±)-laudanosine, m.p. 113–114°, which did not give any depression when mixed with crystals of authentic laudanosine, m.p. 113–114°.

(+)-*Benzoyllaudanidine* D-*tartrate*. Benzoyllaudanine (300 mg) was dissolved in 6 ml of absolute ethanol, 100 mg of D-tartaric acid was added and the suspension was heated to boiling, when all the materials dissolve. On cooling, a solid separated, which after standing several hours at 5°, was filtered off and recrystallized from absolute ethanol (yield 95 mg), m.p. 159–160°. After several recrystallizations from the same solvent, rectangular prisms were obtained, m.p. 160–161°, $[\alpha]_D^{22°}$ +50·5° ± 2° (*c*, 0·4 in chloroform) (Found: C, 61·71; H, 5·97; N, 2·35. Calc. for $C_{31}H_{35}NO_{11}$: C, 62·30; H, 5·86; N, 2·34 per cent).

(−)-*Benzoyllaudanidine* L-*tartrate*. The mother-liquors of the preparation of the D-tartrate were evaporated to dryness. The residue was dissolved in water, and the solution made alkaline with sodium hydrogen carbonate solution and extracted with ether. The ether solution, after being dried and evaporated, left a residue of 150 mg, which was dissolved in 3 ml of boiling absolute ethanol with 50·4 mg of L-tartaric acid. On cooling, a precipitate was obtained, which, after several crystallizations from

[12] O. Hesse, *Liebigs Ann.* Suppl. **8**, 277 (1872), from Beilstein's *Handbuch der Org. Chem.* (4th Ed.) Vol. 21, p. 210. Springer, Berlin (1935).

absolute ethanol, was obtained as rectangular prisms, m.p. 160–161°, $[\alpha]_D^{22°}$ −50·3° ± 1·6° (*c*, 0·34 in chloroform).

(+)-*Benzoyllaudanidine*. (+)-Benzoyllaudanidine D-tartrate (400 mg) was dissolved in 15 ml of saturated sodium hydrogen carbonate solution and the base was extracted with ether. The ether, dried and evaporated, gave an oil that crystallized easily on the addition of one drop of methanol or absolute ether. After being recrystallized several times from ethanol, 240 mg of prisms melting at 144–145° (dec.) were collected, $[\alpha]_D^{22°}$ +63·2 ± 1·4° (Found: C, 72·19; H, 6·48; N, 3·07. Calc. for $C_{27}H_{29}NO_5$: C, 72·46; H, 6·53; N, 3·13 per cent).

(−)-*Benzoyllaudanidine*. Five-hundred milligrams of (−)-benzoyllaudanidine L-tartrate gave 305 mg of (−)-benzoyllaudanidine, m.p. 144–145°, $[\alpha]_D^{22°}$ −63·9 ± 1·6°.

By dissolving equimolecular quantities of the optical isomers of benzoyllaudanidine in boiling absolute ethanol, the racemic (±)-benzoyllaudanidine, m.p. 156–157°, was obtained.

(+)-*Laudanidine* (IV; $R_1 = OH$, $R_2 = CH_3$). (+)-Benzoyllaudanidine (100 mg) was heated for 45 min at 70° with 10 ml of concentrated hydrochloric acid. After cooling, the solution was extracted with ether. The aqueous layer was diluted, made alkaline with sodium hydrogen carbonate solution and extracted again with ether. After drying and evaporating, the oily residue crystallized on the addition of one drop of methanol. On recrystallization several times from methanol, 67 mg of small prisms, m.p. 184–185° (vacuum), were obtained, $[\alpha]_D^{22°}$ −94·8 ± 1·4° (*c*, 0·4 in chloroform) (Found: C, 70·01; H, 7·46; N, 4·07. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08 per cent. For the (+)-laudanidine obtained from laudanosine, Späth and Burger[4] give m.p. 184–185°.

(+)-*Laudanidine picrate* was obtained as prisms from ethanol, m.p. 174–175° (Found: C, 54·92; H, 4·79; N, 9·87. Calc. for $C_{20}H_{25}NO_4.C_6H_3N_3O_7$: C, 54·54; H, 4·93; N, 9·79 per cent.

(−)-*Laudanidine*. One-hundred milligrams of (−)-benzoyllaudanidine was hydrolyzed in the same way as the dextrorotatory isomer. After recrystallization several times from methanol, 69 mg of crystals, m.p. 184–185° (vacuum), were obtained, $[\alpha]_D^{22°}$ −94·7° ± 1·3. The picrate had m.p. 174–175°.

(±)-*Laudanidine* (*laudanine*). Ten milligrams of each optical isomer of laudanidine was dissolved in boiling absolute ethanol. On cooling, the racemic form crystallized, m.p. 164–165°; picrate, m.p. 176–177°.

Benzoylhomovanillic acid. Homovanillic acid (10 g) were dissolved in 100 ml of 6 per cent sodium hydroxide solution and treated with 8·5 g of benzoyl chloride. When benzoylation was complete, 2 N hydrochloric acid was added to pH 3·5. A precipitate was produced, which was filtered off and washed well with water, and the benzoic acid was separated by boiling the solid with 10 ml of water and filtering the solution while hot. By repeating the extraction, an insoluble product, m.p. 167°, was obtained, which was recrystallized from absolute ethanol (yield 13·7 g; 88 per cent), m.p. 169° (Berlin *et al.*[13] give m.p. 169°).

Benzoylhomovanillyl chloride. Benzoylhomovanillic acid (10 g) was boiled with 25 ml of thionyl chloride for 1 hr. The excess of thionyl chloride was removed by distillation and the oily residue was well dried in a desiccator. It was then dissolved in 20

[13] A. Ya. Berlin, S. M. Sherlin and T. A. Serebrennikova, *Zhur. Obshchei Khim.* **19**, 759 (1949); *Chem. Abstr.* **44**, 1058 (1950).

ml of boiling benzene and after cooling, 140 ml of light petroleum boiling range (66–73°) was slowly added and the solution was set aside in a cool room overnight. The chloride crystallized as needles, which were filtered off (yield 8·1 g). The mother-liquors were concentrated to 80 ml and a new crop of chloride (1·5 g) was obtained. The chloride was recrystallized by dissolving in benzene and adding light petroleum when 9·2 g (77 per cent) of product was obtained as prisms, m.p. 64° (Berlin *et al.*[13] give m.p. 66–67°).

4′-Benzoyloxy-3′-methoxyphenyl-N-2-(3,4-*dimethoxyphenyl*)*ethylacetamide* (I; $R_1 = CH_3$, $R_2 = PhCO$). To 6 g of 3,4-dimethoxyphenylethylamine dissolved in 40 ml of chloroform and cooled to 0–5°, 10 g of benzoyl homovanillyl chloride, dissolved in 40 ml of chloroform, was slowly added, the temperature being kept low. After 10 min, 60 ml of N sodium hydroxide was added. The chloroform layer was decanted and well washed with 2 N hydrochloric acid and water. It was then dried and distilled under vacuum. The oily residue crystallized on standing in a desiccator. It was recrystallized from absolute ethanol to give 14·2 g (95 per cent) of needles, m.p. 97°. For analysis it was recrystallized several times from absolute ethanol, m.p. 98°, soluble in acetone and acetic acid, λ_{max} 276 mμ (log ε 3·84) (Found: C, 67·33; H, 6·34; N, 2·91. Calc. for $C_{26}H_{27}NO_6.H_2O$: C, 66·79; H, 6·25; N, 3·00 per cent).

1-(4′-Benzoyloxy-3′-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (II; $R_1 = CH_3$, $R_2 = PhCO$). To 5 g of the amide, dissolved in 50 ml of chloroform and cooled to 0–5°, 10 g of phosphorus pentachloride was slowly added. The temperature was kept at 5° and after 3 hr the suspension was left at room temperature for 4 days. During the first day a precipitate appeared that did not increase in bulk in the remaining time. Then 20 g of crushed ice was added and the mixture was evaporated under vacuum to remove the chloroform. Water and an insoluble solid remained. The water was separated by decanting and the solid was dried. It was dissolved in 60 ml of absolute ethanol and 60 ml of 2 N hydrochloric acid was added. Fine needles of the hydrochloride were obtained, which after recrystallization several times from absolute ethanol (yield 4·5 g; 79 per cent) had m.p. 149°, λ_{max} 276 mμ (log ε 3·94), 308–310 mμ (log ε 3·84) (Found: C, 66·50; H, 6·01; N, 2·89; Cl, 6·95. Calc. for $C_{26}H_{25}NO_5.HCl$: C, 66·72; H, 5·59; N, 2·99; Cl, 7·57 per cent).

1-(4′-Benzoyloxy-3′-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline methiodide. The hydrochloride (4 g) was suspended in 40 ml of water, 20 ml of ethyl ether was added and the suspension was made alkaline by addition of saturated sodium hydrogen carbonate solution. The free base passed into the ether and the extraction was repeated several times. The pooled ether extracts were dried and evaporated to dryness. The colorless residue was dried in a desiccator, 32 ml of methyl iodide was added and the solution was heated to boiling. After 5 min a yellow precipitate appeared and after 30 min the heating was stopped, the excess of methyl iodide was evaporated under vacuum and the residue was crystallized from 200 ml of absolute ethanol, m.p. 198–199°. After three crystallizations from the same solvent the m.p. was 205–206°, as yellow irregular prisms, united to rosettes (yield 3·6 g; 80 per cent) (Found: C, 56·29; H, 5·12; N, 2·49; I, 22·44. Calc. for $C_{26}H_{25}NO_5.CH_3I$: C, 56·56; H, 4·88; N, 2·44; I, 22·15 per cent).

1-(4′-Benzoyloxy-3′-methoxybenzyl)-6,7-dimethoxytetrahydroisoquinoline hydriodide. The dihydro*iso*quinoline methiodide (2 g) was dissolved in 150 ml of boiling absolute ethanol, the solution was cooled, 300 mg of platinum oxide was added and it was

reduced with hydrogen at a pressure of 2 atmospheres. After 30 min, a precipitate of crystalline white needles appeared, which increased with time. After 6 hr the hydrogenation was stopped, the crystalline precipitate was dissolved by heating and the platinum was filtered off. After being kept overnight at 5°, a new crystalline precipitate was obtained, which was filtered off and washed well with absolute ethanol (yield 1·85 g; 92 per cent), m.p. 165–166°, the melting point remained constant after recrystallization from ethanol (Found: C, 56·87; H, 5·92; N, 2·59; I, 22·38. Calc. for $C_{27}H_{29}NO_5.HI$: C, 56·38; H, 5·24; N, 2·46; I, 22·05 per cent).

(±)-*Benzoylpseudocodamine* The hydriodide (500 mg) was suspended in water, saturated sodium hydrogen carbonate solution was added to alkalinity and the liberated base was extracted with ether. The ether extracts were well dried and evaporated in vacuum, to leave a yellowish crystalline residue (343 mg), m.p. 131–132°. It was recrystallized in poor yields from absolute ethanol, when white rectangular prisms with a constant m.p. of 134–135° were obtained. They gave a negative test for phenols (Folin, Molish and diazotized *p*-nitroaniline) and a slight positive Burger's test for pseudocodamine, possible because of small hydrolysis of the benzoyl group; λ_{max} 282 mμ (log ε 3·87) (Found: C, 72·99; H. 6·50. Calc. for $C_{27}H_{29}NO_5$: C, 72·46; H, 6·53 per cent).

(±)-*Pseudocodamine* (IV; $R_1 = CH_3$, $R_2 = H$). The benzoyl base (150 mg) was suspended in 15 ml of concentrated hydrochloric acid and heated for 45 min at 70° in a water bath. The base dissolves easily. After heating, the solution was extracted with ether, to remove the benzoic acid. It was then diluted with water and made alkaline with sodium hydrogen carbonate solution, and the base was extracted with ether. The ether extracts were united, washed with water, dried and evaporated. The yellowish crystalline residue was crystallized several times from *cyclo*hexane, when white needles united to rosettes, of constant m.p. 131–132°, were obtained; the product was very soluble in methanol, ethanol, acetone and chloroform, but less soluble in benzene and *iso*propyl ether. It gives a positive Folin and Cinocalteu reaction and couples with diazotized-*p*-nitroaniline. When dissolved in concentrated sulfuric acid, a violet color appears on adding a small crystal of potassium dichromate (Burger's reaction); Millon's reaction is negative; λ_{max} 284 mμ (log ε 3·78) (Found: C, 69·90; H, 7·05; N, 4·18. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08 per cent).

Burger[10] gives m.p. 129–130° for the (±)-pseudocodamine prepared from (±)-laudanosine.

(±)-Pseudocodamine picrate was prepared in the usual way in ethanol solution to give rectangular plates, m.p. 156–157°, with sintering from 153° (Found: C, 54·69; H, 5·24; N, 9·85. Calc. for $C_{20}H_{25}NO_4.C_6H_3N_3O_7$: C, 54·54; H, 4. 93; N, 9·79 per cent).

The hydriodide was obtained as needles from ethanol, m.p. 213–214° (Found: C, 50·86; H, 5·57; I, 26·27. Calc. for $C_{20}H_{25}NO_4.HI$: C, 50·95; H, 5·52; I, 26·94 per cent).

(+)-*Benzoylpseudocodamine* D-*tartrate*. *rac*.-Benzoylpseudocodamine (300 mg) was dissolved in 6 ml of warm absolute ethanol and a solution of 100 mg of D-tartaric acid in 6 ml of warm absolute ethanol was added. On cooling, a crystalline precipitate appeared, which was filtered off and recrystallized six times from absolute ethanol to give rectangular plates, m.p. 186–187°, with sintering from 183°, $[\alpha]_D^{22°}$ −40·7 ± 2° (*c*, 0·38 in chloroform) (Found: C, 61·47; H, 5·95; N, 2·41. Calc. for $C_{31}H_{35}NO_{11}$: C, 62·30; H, 5·86; N, 2·34 per cent).

(−)-*Benzoylpseudocodamine* L-*tartrate*. From the mother-liquors of the separation

of (+)-benzoylpseudocodamine D-tartrate, the base was extracted with ether in the usual way. By evaporation of the ether extracts, 100 mg of a residue was obtained and purified by recrystallization from ethanol, when 100 mg of a product m.p. 132° was obtained. This was dissolved, together with 34 mg of L-tartaric acid, in 2 ml of boiling absolute ethanol. On cooling, rectangular plates separated, which were filtered off and recrystallized four times from absolute ethanol, m.p. 186–187°, sintering from 183°, $[\alpha]_D^{22°}$ −41·1° ± 2° (*c*, 0·38 in chloroform).

(+)-*Benzoylpseudocodamine*. (+)-Benzoylpseudocodamine D-tartrate (500 mg) was suspended in 20 ml of water, and the suspension was made alkaline with sodium hydrogen carbonate and extracted with ether. The ether extracts on evaporation gave (+)-benzoylpseudocodamine, which was recrystallized several times from methanol to give long rectangular plates (yield 290 mg; 88 per cent), m.p. 134°, $[\alpha]_D^{22°}$ 35·3 ± 1·4° (*c*, 0·4 in chloroform).

(−)-*Benzoylpseudocodamine*. (−)-Benzoylpseudocodamine L-tartrate (300 mg) was treated as described for the dextrorotary isomer, when the yield was 180 mg (90 per cent) of (−)-benzoylpseudocodamine, m.p. 133–134°, $[\alpha]_D^{22°}$ −34·8° ± 2° (*c*, 0·6 in chloroform).

(+)-*Pseudocodamine*. (+)-Benzoylpseudocodamine (150 mg) was hydrolyzed as has been described for the racemic benzoyl base. After elimination of the benzoic acid, the ether extracts gave on evaporation an oil, which crystallized when a drop of absolute ether was added; a crude product was obtained, m.p. 124–125,° which after three crystallizations from *cyclo*hexane gave long prisms, m.p. 131–132°, $[\alpha]_D^{22°}$ +24·7° ± 2° (*c*, 0·46 in chloroform, soluble in cold methanol, ethanol and acetone, but less soluble in ether (Found: C, 69·85; H, 7·22; N, 4·06. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08 per cent).

The picrate was obtained as rectangular plates, m.p. 194–195° (from ethanol) (Found: C, 54·68; H, 4·58; N, 9·59. Calc.: C, 54·54; H, 4·93; N, 9·79 per cent).

(+)-*Laudanosine from* (+)-*pseudocodamine*. (+)-pseudocodamine (100 mg) was dissolved in 10 ml of ether, treated with a solution of diazomethane and left overnight at 5°. After destruction of the excess of diazomethane with acetic acid, the ether was evaporated and the solid residue was extracted with boiling light petroleum (boiling range 30–60°). On cooling prisms united to rosettes, m.p. 81°, were obtained, which were recrystallized several times from light petroleum (boiling range 30–60°), m.p. 89°, $[\alpha]_D^{22°}$ +52·2° ± 1·3° (in chloroform. (+)-Laudanosine has m.p. 89° and $[\alpha]_D$ +52° (in chloroform).

(−)-*Pseudocodamine*. (−)-Benzoylpseudocodamine (150 mg) was hydrolyzed in a similar way to the *dextro* isomer, when 115 mg of the crude base, m.p. 126°, were obtained, which after several recrystallizations from *cyclo*hexane had m.p. 131–132°, the picrate was obtained as rectangular plates, m.p. 194–195° (from ethanol), $[\alpha]_D^{22°}$ − 24·4° ± 2°.

Acknowledgements—We thank Prof. P. A. Plattner, Hoffman-La Roche, Basel (Switz.), for a generous gift of *iso*vanillin, Prof. Alfred Burger, Charlottesville, Virginia, for personal information on his thesis, and Mr. Joseph F. Alicino, the Squibb Institute for Medical Research, New Brunswick, N.J., for the microanalyses.

Tetrahedron, 1958, Vol. 4, pp. 351–360. Pergamon Press Ltd., London

ASPECTS OF STEREOCHEMISTRY—I*

PROPERTIES AND REACTIONS OF SOME DIOLS

J. S. BRIMACOMBE, A. B. FOSTER, M. STACEY and D. H. WHIFFEN
Chemistry Department, The University, Birmingham

(*Received* 5 *June* 1958)

Abstract—The extent of intramolecular hydrogen-bonding, as determined by infra-red spectroscopy in the hydroxyl stretching region, in certain vicinal diols of *cyclo*hexane, *cyclo*pentane, tetrahydropyran and tetrahydrofuran and in related compounds provides evidence for the stabilities of different conformations. In certain compounds these stabilities can be affected by hydrogen bonding from a substituent hydroxyl group to a ring oxygen. Additional evidence is provided in the case of the tetrahydropyran diols by $[M]_D$ values. The rate of reaction of the vicinal diols of these cyclic systems with glycol splitting reagents, and their zone electrophoretic mobility in an alkaline borate buffer is influenced by the presence of a ring oxygen.

MUCH information is available concerning inter and intramolecular hydrogen bonding[1,2] in saturated carbocyclic vicinal diols and the reactivity of these compounds towards glycol splitting reagents.[1a,3] Little is known, however, of the effect, on these properties, of replacing a ring methylene group by oxygen to yield compounds derived from tetrahydropyran and tetrahydrofuran. Some consequences of this replacement are noted herein.

The diols studied are listed in Table 1. With the exception of *cyclo*hexane *trans*-1 : 2-diol (which was obtained *via* epoxidation[4] of *cyclo*hexene) the carbocyclic *trans*-diols were prepared by bromination of the corresponding olefins, solvolysis of the *trans*-dibromides with dry acetic acid and silver acetate and saponification of the resultant *trans*-diacetates. This reaction sequence which was used by Winstein and Roberts[5] for the synthesis of indan *trans*-1:2-diol appears to be a general method. The carbocyclic *cis*-diols were obtained by hydroxylation of the appropriate olefins with permanganate.[6] Evidence of the homogeneity of the carbocyclic diols, as prepared by these methods, was obtained by the application of zone electrophoresis (ionophoresis) in borate buffer (pH 10) using the enclosed strip technique[7] under

I

II

* A preliminary report of some of these results has been given Abstr. Papers Amer. Chem. Soc. Meeting, New York, September 1957, p. 2D.

[1a] L. P. Kuhn, *J. Amer. Chem. Soc.* **74**, 2492 (1952); [b] *Ibid.* **76**, 4323 (1954).

[2] A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.* 4391 (1956).

[3] See H. H. Wasserman, *Steric Effects in Organic Chemistry* (Edited by M. S. NEWMAN) p. 378. Academic Press (1956). See also references cited therein.

[4] A. Roebuck and H. Adkins, *Organic Syntheses* Collective Vol. 3, p. 217.

[5] S. Winstein and R. M. Roberts, *J. Amer. Chem. Soc.* **75**, 2297 (1953).

[6] M. F. Clarke and L. N. Owen, *J. Chem. Soc.* 315 (1949).

[7a] H. G. Kunkel and A. Tiselius, *J. Gen. Physiol.* **35**, 89 (1951); [b] A. B. Foster, *Chem. & Ind* 1050 (1952).

standard conditions[7b] when, with one exception, each diol gave a single compact zone; *cyclo*pentane *cis*-1:2-diol appeared to contain a trace of the *trans*-isomer.

Synthesis of 1:5-anhydro 2-deoxy-D-*threo*pentitol* (I) [1:5-anhydro 4-deoxy-D-*threo*pentitol, (-)-tetrahydropyran 3/4-diol] was accomplished by platinum catalysed hydrogenation of 3:4-di-O-acetyl-D-xylal followed by saponification of the product. Alternatively 3:4-di-O-acetyl-D-xylal may be catalytically deacetylated (Zemplén) and the D-xylal so obtained hydrogenated to yield the diol (I). The *cis*-isomer 1:5-anhydro 2-deoxy-L-*erythro*pentitol [1:5-anhydro 4-deoxy-D-*erythro*pentitol, (+)-tetrahydropyran/3, 4-diol] was obtained by sequential application of platinum catalysed hydrogenation and saponification to 3:4-di-O-acetyl-L-arabinal. Racemic forms of the diols (II) and (I) have previously been obtained by *cis*- and *trans*-hydroxylation of 2:3-dihydropyran[8] and by hydrogenolysis of methyl β-L-arabinopyranoside.[9] Dehydration of L-threitol and erythritol with sulphuric acid gave respectively 1:4-anhydro-L-threitol (threitan) and 1:4-anhydro-erythritol (erythritan).

The inter- and intra-molecular hydrogen bonding which may occur in dry carbon tetrachloride solutions of carbocyclic and acyclic diols has been intensively studied.[1,2] Intermolecular hydrogen bonding is critically dependent on the concentration of the diol and becomes negligible in solutions which are less than 0·005 M with respect to diol.[1] The infra-red spectral data in Table 1 were determined on solutions of the diols in dry carbon tetrachloride below this critical concentration. Under these conditions the absorption at ca. 3630 cm^{-1} has been associated[1] with free hydroxyl groups and that at ca. 3580 cm^{-1} with intra-molecularly hydrogen-bonded hydroxyl groups.† Kuhn[1] considers that the magnitude of $\Delta\nu$, the arithmetical difference between the free and bonded hydroxyl absorption frequencies for a given diol, is proportional to the strength of the hydrogen bond and hence an indication of the O-O distance in the diol. Cole and Jefferies[2] prefer to express $\Delta\nu$ as the difference between a standard secondary hydroxyl absorption frequency (3629 cm^{-1}) and the bonded hydroxyl absorption frequency. Both values of $\Delta\nu$ are recorded in Table 1. Further, as Cole and Jefferies have emphasised,[2] the extent of intramolecular hydrogen bonding may be approximately assessed from the relative extinction coefficients of the free and bonded hydroxyl groups and, together with $\Delta\nu$ values, this information constitutes direct experimental evidence on which the allocation of conformation to the diols in carbon tetrachloride solution may be based. The molecular extinction coefficients are included in parentheses in Table 1.

In considering six membered ring systems it is now accepted[11] that, in *cyclo*hexane derivatives at ordinary temperatures, the chair form will be preferred to other possible conformations. Further, in derivatives containing substituents of similar bulk, because of non-bonded interactions, the preferred chair forms will in general be those with the greatest possible number of equatorial substituents. It seems most probable[12] that similar considerations will apply to derivatives of tetrahydropyran and 1:3-dioxan.

* The orientation adopted for formulae (I) and (II), and hence the nomenclature, best illustrates the relationship of these compounds to the carbohydrate precursors.

† Subsequently referred to as bonded hydroxyl groups.

[8] O. Heuberger and L. N. Owen, *J. Chem. Soc.* 910 (1952).

[9] H. F. Bauer and D. E. Stuetz, *J. Amer. Chem. Soc.* **78**, 4097 (1956).

[10a] R. Montgomery and L. F. Wiggins, *J. Chem. Soc.* 390 (1946); [b]L. F. Wiggins, *Ibid.* 4 (1945); [c]*Ibid.* 1403 (1947).

[11] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956) and references cited therein.

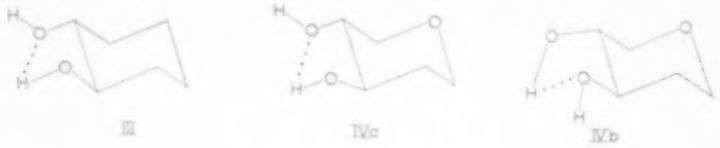
[12] J. A. Mills, *Adv. Carbohydrate Chem.* **10**, 1 (1955).

TABLE 1. INFRA-RED SPECTRAL, GLYCOL CLEAVAGE AND IONOPHORETIC DATA ON CERTAIN DIOLS AND RELATED COMPOUNDS

Compound	Infra-red absorption (cm^{-1})[a]		$\Delta\nu$[b]	$\Delta\nu$[c]	Periodate oxidation ($t\frac{1}{2}$)	Lead tetra-acetate oxidation ($t\frac{1}{2}$)	M_G
	Free OH	Bonded OH					
*cyclo*Hexane *trans*-1:2-diol	3633 (55)[d]	3602 (70)[d]	31	27	rapid	1·9 hr	0·00
1:5-Anhydro 2-deoxy-D-*threo*pentitol (I)	3633 (56)	3608 (52)	25	21	20 min	5hr	0·00
*cyclo*Hexane *cis*-1:2-diol	3632 (58)[e]	3592 (62)[e]	40	37	rapid	5 min	0·07
1:5-Anhydro 2-deoxy-L-*erythro*pentitol (II)	3633 (25)	3583 (58)	50	46	rapid	9 min	0·23
*cyclo*Pentane *trans*-1 : 2-diol	3624	—			5 min	10 min	0·00
1:4-Anhydro-L-threitol (L-threitan)	3624	—				11 hr	0·00
*cyclo*Pentane *cis*-1 : 2-diol	3624 (50)	3579 (50)	45	50	rapid	rapid	0·69
1:4-Anhydroerythritol (erythritan)	3624 (40)	3585 (40)	39	44		rapid	0·88
1:4-3 : 6-Dianhydro-D-glucitol[f] (XII)	3624	3540	84	89			
1:4-3 : 6-Dianhydro-D-mannitol[f] (XIII)	—	3540		89			
1:4-3 : 6-Dianhydro-L-iditol[f,g] (XIV)	3624	—					
Indan *trans*-1:2-diol	3624	—			60 min		0·00
Indan *cis*-1:2-diol	3620 (43)	3579 (60)	41	50	rapid		0·72
*cyclo*Heptane *trans*-1:2-diol	3626[h]	3589[h]	37	40	rapid		0·53
*cyclo*Heptane *cis*-1:2-diol	3632[h]	3588[h]	44	41	rapid		0·69
1:3-Dioxan-5-ol (1:3-O-methylidene glyceritol)	3635 (25)	3593 (100)	42	36			

[a] Figures in parentheses refer to maximum extinction coefficients (ε).
[b] Arithmetical difference between absorption frequencies of free and bonded hydroxyl groups.
[c] Arithmetical difference[2] between absorption frequencies of standard secondary (3629 cm^{-1}) and bonded hydroxyl groups.
[d] Cole and Jefferies[2] record 3631 (62) and 3600 (75).
[e] Cole and Jefferies[2] record 3626 (60) and 3588 (60).
[f] These compounds are described in the literature.[10]
[g] Reported[10c] as a hemihydrate; obtained anhydrous by distillation.
[h] Data taken from ref. 2.

*cyclo*Hexane *trans*-1:2-diol and 1:5-anhydro-2-deoxy-D-*threo*pentitol (I) showed absorption for free hydroxyl groups at 3633 cm^{-1} and bonded hydroxyl groups at 3602 cm^{-1} and 3608 cm^{-1} respectively. The extinction coefficients indicate that, in each diol, essentially one hydroxyl group is free and one is bonded.



III IVa IVb

V VI

Thus for *cyclo*hexane *trans*-1:2-diol the conformation (III) (and also the enantiomorphous structure) with both hydroxyl groups in equatorial positions must predominate as expected on theoretical grounds,[11] since bonding would not be possible in the alternative chair conformation, which has both hydroxyl groups in axial positions. The situation is more complex for 1:5-anhydro-2-deoxy-D-*threo*pentitol (I) which may exist in the chair conformations (IVa), (IVb) and (V) in each of which one hydroxyl group may be free and one bonded. On theoretical grounds[11] the conformations (IV) should be preferred to conformation (V). Although one hydroxyl group may be bonded in each case, adverse non-bonded interactions would be lower in the conformations (IV) (equatorial hydroxyl groups) than in conformation (V) (axial hydroxyl groups).

Some support for this view follows from the observation[13] that, in carbon tetrachloride solution, an appreciable percentage of the hydroxyl group in tetrahydropyran-3-ol is not bonded to the ring oxygen indicating that the intramolecular hydrogen bonding is not strong enough to fix the conformation. Intramolecular hydrogen

VII VIII

IXa IXb

[13] S. A. Barker, A. B. Foster, D. H. Whiffen and G. Zweifel, Unpublished results.

bonding in the conformation (VI) of tetrahydropyran-3-ol would be expected to be less sterically hindered than in conformation (V) of 1:5-anhydro-2-deoxy-D-*threo*pentitol.

On the available evidence the two arrangements (IVa) and (IVb) cannot be distinguished.

The similar extinction coefficients of free and bonded hydroxyl groups in *cyclo*hexane-*cis*-1:2-diol indicates the presence of one free and one bonded hydroxyl group as in conformation (VII). The two possible chair conformations of *cyclo*hexane-*cis*-1:2-diol are enantiomorphous and will occur to an equal extent in carbon tetrachloride solution. Conformation (VII) has a bonded equatorial hydroxyl group but it should be noted that the alternative arrangement with a bonded axial hydroxyl group is also feasible. A distinction between these possibilities is not permitted on the available data.

The extinction coefficients for 1 : 5-anhydro-2-deoxy-L-*erythro*pentitol of 25 and 58 respectively for free and bonded hydroxyl groups suggest that both hydroxyl groups are simultaneously hydrogen bonded to an appreciable extent. 1:5-Anhydro-2-deoxy-L-*erythro*pentitol (II) may exist in the chair conformations (VIII) and (IX) each of which contain one axial and one equatorial hydroxyl group. Hydrogen bonding is possible between the hydroxyl groups in each conformation but in conformation (VIII) an additional hydrogen bond may be formed between the axial $C_{(4)}$-hydroxyl group and the ring oxygen. The infra-red data are consistent with the predominance of the chair form (VIII) in the conformational equilibrium. The possible close proximity of the hydrogen of the $C_{(4)}$-hydroxyl group in conformations (VI) and (VIII) and the ring oxygen may be clearly seen in accurate scale models. The presence of some absorption associated with free hydroxyl groups in the spectrum of 1:5-anhydro-2-deoxy-L-*erythro*pentitol (II) may be due either to incomplete hydrogen bonding in conformation (VIII) or to the existence of a part of the diol in the alternative chair conformations (IX) where the ring oxygen cannot participate in intramolecular hydrogen bonding.

TABLE 2. OBSERVED AND CALCULATED $[M]_D$ VALUES FOR CERTAIN PYRAN DERIVATIVES

Diol	Conformation	$[M]_D$ Calc. (parameters)[a]	Obs.
1:5-Anhydro-2-deoxy-D-*threo*pentitol (I)	HO-groups axial (V)	−43° (−I)	−35°
	HO-groups equatorial (IV)	−45° (−F)	
1:5-Anhydro-2-deoxy-L-*erythro*pentitol (II)	$C_{(3)}$-HO-group axial (IX)	−45°(−F)	
	$C_{(4)}$-HO-group axial (VIII)	+88° (+I + F)	+75°

[a] Parameters are those evaluated by Whiffen.[14]

Using the parameters evaluated by Whiffen,[14] the molecular rotations ($[M]_D$) in aqueous solution of the possible chair conformations of 1:5-anhydro-2-deoxy-D-*threo*pentitol (I) and 1:5-anhydro-2-deoxy-L-*erythro*pentitol (II) may be calculated (Table II). In the case of the *trans*-diol (II) the calculated values for the conformations

[14] D. H. Whiffen, *Chem. & Ind.* 964 (1956).

(IV) and (V) are —45° and —43° respectively (observed —35°); their similarity precludes the use of optical rotation measurements as a means of estimating the percentage of the respective chair forms in the conformational equilibrium. However the observed $[M]_D$ value of +75° for the *cis*-diol (II) indicates that the conformation (VIII) (calc. $[M]_D$ +88°) predominates over conformation (IX) (calc. $[M]_D$ —45°) in the conformational equilibrium.

X XI

In only one (X) of the chair conformations (X) and (XI) of 1:3-dioxan-5-ol (1:3-O-methylidene glyceritol) can the hydroxyl group participate in intramolecular hydrogen bonding with the ring oxygens. The data in Table 1 show that, in carbon tetrachloride solution, not only does intramolecular hydrogen bonding occur but that most of the hydroxyl groups are bonded. Clearly, determination of the extent of intramolecular hydrogen bonding may be of potential value in the allocation of structure to *cis*- and *trans*-forms of 2-C-substituted 1:3-dioxan-5-ol (e.g. 1:3-O-alkylidene and 1:3-O-arylidene glyceritols) since bonding will be sterically hindered in the *trans*-form. Structures have been allocated in this way to the *cis*- and *trans*-forms of 2-C-phenyl 1:3-dioxan-5-ol (1:3-O-benzylidene glyceritols) and will be discussed in detail elsewhere.[15]

XII $R^2 = R^3 = OH$, $R^1 = R^4 = H$

XIII $R^2 = R^4 = OH$, $R^1 = R^3 = H$

XIV $R^1 = R^3 = OH$, $R^2 = R^4 = H$

The infra-red spectrum data (Table 1) for *cyclo*pentane *cis*-1:2-diol and 1:4-anhydro-L-threitol (L-threitan) are closely similar as are those of *cyclo*pentane *trans*-1:2-diol and 1:4-anhydroerythritol (erythritan). Intramolecular hydrogen bonding is possible only in the *cis*-diols. The high $\Delta\nu$ values reflect the close proximity of the hydroxyl groups although they are not in truly eclipsed positions.[16] The series of 1:4-3:6-dianhydrohexitols illustrates the influence of structure on intramolecular hydrogen bonding and emphasises the potential value of these observations in structural determination. The $C_{(2)}$- and $C_{(3)}$-, $C_{(1)}$- and $C_{(5)}$-oxygen bonds in 1:4-3:6-dianhydro-L-iditol (XIV) are *trans*-related as in L-threitan so that intramolecular hydrogen bonding is precluded. A *cis*-relation of the $C_{(2)}$- and $C_{(3)}$-oxygen bonds

[15] J. S. Brimacombe, A. B. Foster and M. Stacey, *Chem. & Ind.* 1228 (1958).
[16] H. Kwart and W. G. Vosburgh, *J. Amer. Chem. Soc.* **76**, 5400 (1954).

exists in the D-mannitol analogue (XIII) permitting a single intramolecular hydrogen bond. In the D-glucitol compound (XII) two intramolecular hydrogen bonds may occur and the absence of detectable absorption for free hydroxyl groups indicates the completeness of the hydrogen bonding.

The influence of structure on the rate of reaction of carbocyclic vicinal diols with lead tetra-acetate has been studied in detail.[3] A comparison of the rates of attack, by lead tetra-acetate, and sodium metaperiodate on the five and six membered cyclic diols is recorded in Table 1. In those cases where the rate of oxidation was sufficiently slow to follow kinetically, replacement of a ring methylene group by oxygen was observed to retard the rate of attack by the glycol splitting reagents. The effect was especially marked in 1:4-anhydro-L-threitol.

The M_G values (relative mobilities[17]) recorded in Table 1 were obtained by zone electrophoresis (ionophoresis) of the diols in borate buffer at pH 10 using the enclosed strip technique.[7] With one exception all the vicinal *trans*-diols showed zero mobility; the high M_G value of *cyclo*heptane *trans*-1:2-diol indicates an extensive reaction with borate ions to form the negatively charged complex[18] which migrates in the electric field. Complex formation is most likely permitted by the flexibility of the seven membered ring. This flexibility, also enables *cyclo*heptane *trans*-1:2-diol to form an *iso*propylidene derivative[19] and an osmate complex.[20]

All the vicinal *cis*-diols so far studied show a definite mobility under the adopted experimental conditions. Replacement of a ring methylene group by oxygen appears to facilitate complex formation and confers a higher M_G value. This effect is most noticeable in 1:5-anhydro 2-deoxy-L-*erythro*pentitol which has an M_G value (0·23) much higher than the carbocyclic analogue, *cyclo*hexane *cis*-1:2-diol (0·07).

EXPERIMENTAL

cyclo*Heptane* trans-1 : 2-*diol*

Bromine was added slowly to a cooled (0°) solution of *cyclo*heptene (12 g) in ether (40 ml) until the bromine colour persisted. After washing successively with 0·01N-sodium hydroxide and water the dried ($MgSO_4$) ethereal solution was concentrated. From the residue *cyclo*heptane *trans*-1:2-dibromide[21] (25·4 g, 79·4%) was obtained as a colourless liquid b.p. 138–140° (bath)/20–25 mm, $n^{23·5}$ 1·5532.

A suspension of silver acetate (40 g) in glacial acetic acid (80 ml) was treated with acetic anhydride (25 ml) at 110° for 2 hr. The dibromide (25·4 g) was then added to this mixture and the temperature maintained at 110° for 15 hr. Thereafter insoluble material was removed, the filtrate evaporated and *cyclo*heptane *trans* 1:2-diacetate (8·2 g, 40·4%) was obtained as a colourless liquid b.p. 99–101° (bath)/0·5 mm, n^{23} 1·4530.

The diacetate (4 g) was saponified by treatment for 2 hr with a boiling mixture of ethanol (8 ml) and aqueous sodium hydroxide (8 ml, 35% w/v). After dilution with water (8 ml) the reaction solution was extracted with ether continuously during 1 day. Evaporation of the extract yielded *cyclo*heptane *trans* 1 : 2-diol (1·43 g, 74%) after

[17] A. B. Foster, *J. Chem. Soc.* 982 (1953).
[18] H. S. Isbell, J. F. Brewster, N. B. Holt and H. L. Frush, *J. Res. Nat. Bur. Stand.* **40**, 129 (1948).
[19] H. G. Derx, *Rec. Trav. Chim.* **41**, 312 (1922).
[20] R. Criegee, B. Marchand and H. Wannowius, *Liebigs Ann.* **550**, 111 (1942).
[21] R. Willstätter, *Liebigs Ann.* **317**, 204 (1901).

isolation as a colourless liquid b.p. 100° (vapour)/0·50 mm which solidified on cooling, m.p. 60–62° without recrystallisation.[18]

Indan *trans*-1:2-diol,[5] m.p. 156–157° and *cyclo*pentane trans-1:2-diol[5] b.p. 131°/15–20 mm were prepared from the appropriate olefins by the above general procedure. *cyclo*Hexane *trans*-1:2-diol, m.p. 102–103° was prepared by the method of Roebuck and Adkins.[4]

Preparation of cis-*diols*

The general method described by Clarke and Owen[6] when applied to the appropriate olefins gave *cyclo*hexane *cis*-1:2-diol[6] (14%), m.p. 93–94°, *cyclo*heptane cis-1 : 2-diol[18] (11%) m.p. 45–46°, *cyclo*pentane *cis*-1:2-diol[18] (11%) b.p. 133° (vapour)/29 mm, and indan *cis*-1:2-diol[5] (10·8–14·5%), m.p. 96–98°. The m.p.'s are in good agreement with those reported in the literature.

3:4-*Di*-O-*acetyl* 1:5-*anhydro* 2-*deoxy*-D-threo*pentitol*

A solution of 3:4-di-O-acetyl-D-xylal [3 g, m.p. 36–38°, $[\alpha]_D^{20}$ −288°(*c*, 1·0 in water), prepared according to the method of Overend, Shafizadeh and Stacey[22]] in aqueous alcohol (100 ml, 1:1 v/v) in which was suspended platinum oxide (100 mg) was shaken in an atmosphere of hydrogen at a slight over pressure at room temperature. Absorption of hydrogen was complete within 30 min and after removal of catalyst and solvents the *product* (1·3 g, 43%) was isolated as a colourless liquid b.p. 102° (vapour)/0·5 mm, $[\alpha]_D^{20}$ −38°(*c*, 0·85 in $CHCl_3$), $[M]_D$ −77° (Found: C, 54·1; H, 6·6. $C_9H_{14}O_5$ requires C, 53·4; H, 6·9%).

1:5-*Anhydro*-2-*deoxy*-D-threo*pentitol*

A solution of 3:4-di-O-acetyl 1:5-anhydro-2-deoxy-D-*threo*pentitol (1·4 g) in 6 N-sodium hydroxide (8 ml) and ethanol (8 ml) was boiled under reflux for 2 hr. After removal of sodium ions by Amberlite [IR-120 (H^+)] and evaporation of the solvents the product was isolated as a colourless liquid b.p. 75–80° (vapour)/0·5 mm which crystallised on storage to yield a very hygroscopic solid (0·5 g, 60·7%) m.p. 69° (without recrystallisation), $[\alpha]_D^{20}$ −29·6° (*c*, 2·5 in water), $[M]_D$ −35° (Found: C, 50·6; H, 8·6. $C_5H_{10}O_3$ requires C, 50·8; H, 8·5%).

3:4-*Di*-O-*acetyl*-1:5-*anhydro*-2-*deoxy*-L-erythro*pentitol*

A solution of 3:4-di-O-acetyl-L-arabinal [3·2 g, b.p. 110–140° (vapour)/0·01 mm, $[\alpha]_D^{20}$ −236° (*c*, 1·12 in $CHCl_3$), prepared according to the method of Deriaz *et al.*[23]] was hydrogenated and isolated as for the *threo* isomer to yield the product (2·2 g, 67%), b.p. 86–90° (vapour)/0·2 mm, $[\alpha]_D^{20}$ +75° (*c*, 1·0 in H_2O) $[M]_D$ +151°. (Found; C, 53·6; H, 6·9. $C_9H_{14}O_5$ requires C, 53·4; H, 6·9%).

1:5-*Anhydro*-2-*deoxy*-L-erythro*pentitol*

(*a*) 3:4-Di-O-acetyl-1:5-anhydro-2-deoxy-L-*erythro*pentitol (1·4 g) was saponified as for the *threo* isomer and the product (0·5 g, 60·7%) isolated as a colourless liquid b.p. 120° (vapour)/0·2–0·3 mm, $[\alpha]_D^{20}$ +64° (*c*, 1·5 in water), $[M]_D$ +75°. (Found: C, 51·2; H, 8·9. $C_5H_{10}O_3$ requires C, 50·8; H, 8·5%).

[18] W. G. Overend, F. Shafizadeh and M. Stacey, *J. Chem. Soc.* 671 (1950).
[22] R. E. Deriaz, W. G. Overend, M. Stacey, E. G. Teece and L. F. Wiggins, *J. Chem. Soc.* 1879 (1949).

(*b*) A solution of L-arabinal [0·8 g, m.p. 80–82°, $[\alpha]_D^{20}$ −202° (*c*, 3·0 in water) prepared according to the method of Deriaz *et al.*[23]] in aqueous ethanol (20 ml, 1:1 v/v) was shaken at room temperature in an atmosphere of hydrogen at slight over pressure and in the presence of platinum oxide (50 mg). Hydrogen absorption was complete within 1 hr and after removal of catalyst and evaporation of the solvents 1:5-anhydro-2-deoxy-L-*erythro*pentitol (0·57 g, 70·4%) was isolated as a colourless liquid b.p. 118–120° (vapour)/0·2–0·3 mm with physical constants identical to those of the product from (*a*).

1:4-*Anhydro*-L-*threitol*

A solution of butyl L-tartrate (10 g, $n^{16.5}$1·4450, $[\alpha]_D^{20}$ +10·2°) in dry tetrahydrofuran (50 ml) was slowly added to a well stirred mixture of lithium aluminium hydride (6 g) in tetrahydrofuran (150 ml) and ether (75 ml) and the final solution boiled under reflux for 1·5 hr. Thereafter the mixture was decomposed by the addition of water (200 ml) the precipitate removed by centrifugation, washed with water and the combined supernatants evaporated. The residue was dissolved in aqueous methanol (200 ml, 1 : 1 v/v) and the solution neutralised with CO_2. After removal of insoluble inorganic material and evaporation of the filtrate L-threitol was obtained as a colourless glass which failed to crystallise. It was therefore dissolved in aqueous sulphuric acid (20 ml, 1 : 1 v/v) and shaken during 1 hr with benzaldehyde (15 ml). After dilution of the reaction mixture with water, the crystalline precipitate was collected, washed with water and recrystallised from toluene to yield 1:2:3:4-di-O-benzylidene-L-threitol[24] (2·2 g), m.p. 215–217°, $[\alpha]_D^{25}$ +81° (*c*, 0·5 in $CHCl_3$).

The dibenzylidene derivative (2·2 g) was hydrolysed by treatment with a boiling mixture of N-sulphuric acid (10 ml) and ethanol (30 ml) for 30 min. The hydrolysate was concentrated, extracted with ether and freed from anions with Amberlite IRA–400 (HO^-) and concentrated. Recrystallisation of the residue gave L-threitol[24] (0·5 g) m.p. 88–89°, $[\alpha]_D^{20}$ −4° (*c*, 8·0 in water).

L-Threitol (2·17 g) was treated with a mixture of water (2·2 g) and sulphuric acid (2·2 g) in a sealed tube at 120° for 1 day. After dilution of the hydrolysate with water (75 ml) anions were removed with Amberlite IRA-400 (HO^-) and the solution concentrated. 1:4-Anhydro-L-threitol (L-threitan) was obtained from the residue as a hygroscopic colourless liquid (1·1 g) b.p. 120° (vapour)/15–17 mm which solidified on storage, m.p. 63–64° (without recrystallisation), $[\alpha]^{20}$ −4° (*c*, 7·2 in water). Klosterman and Smith[24] quote $[\alpha]_D^{25} = -5°$ (in water).

1:4-*Anhydro erythritol*

A solution of erythritol (3 g) in water (3 g) and sulphuric acid (3 g) was heated in a sealed tube for 2 days at 120°. 1:4-Anhydro erythritol (1·3 g) isolated as for the *threo*-isomer was obtained as a colourless hygroscopic liquid b.p. 144° (vapour)/2–3 mm n^{20}1·4767. Klosterman and Smith[24] quote n_D^{24} 1·4370 for this compound.

Zone electrophoresis of diols

The zone electrophoretic (ionophoretic) mobility of the diols in Table 1 were determined using the apparatus and technique described by Foster[7b] with a borate buffer[25] of pH 10. The mobility is given as an M_G value which is defined as the

[24] H. Kolsterman and F. Smith, *J. Amer. Chem. Soc.* **74**, 5336 (1952).
[25] A. B. Foster, P. A. Newton-Hearn and M. Stacey, *J. Chem. Soc.* 30 (1956).

mobility of a substance relative to that of D-glucose under standard conditions (see Foster[26] for a detailed discussion).

Oxidation of diols

(a) *With periodate.* A solution of the diol (0·43 m-mole, 50 mg) in water (5 ml) was treated with 0·05 M aqueous sodium metaperiodate (15 ml) and the volume rapidly adjusted to 100 ml, all solutions being kept at 0°. Aliquots were withdrawn at suitable time intervals and unchanged oxidant determined by the standard arsenite method.[27] In those cases where the rate of reaction was slow enough to follow the times ($t\frac{1}{2}$) of half oxidation of the diols was determined and recorded in Table 1.

(b) *With lead tetra-acetate.* A solution of the diol (26 mg) in glacial acetic acid was adjusted to 20° and treated with a 0·1315 N-solution (49 ml) of lead tetra-acetate in glacial acetic acid also at 20°. The volume was rapidly adjusted to 50 ml. At suitable time intervals unconsumed oxidant was determined in aliquots (5 ml) by a standard procedure.[28] In those cases where oxidation was not too fast the time ($t\frac{1}{2}$) of half oxidation was determined and recorded in Table 1.

1:3-*Dioxan*-5-*ol* (1:3-O-*methylidene glyceritol*)

This compound was obtained as a colourless liquid b.p. 82° (vapour)/11 mm, n^{20} 1·4533 using the method of Hibbert and Carter[29] who quote similar physical constants.

Methylation of this compound as described by Hibbert and Carter[29] gave 5-O-methyl 1:3-dioxan-5-ol (2-O-methyl 1:3-O-methylidene glyceritol) b.p. 147° (vapour)/760 mm, n^{25}1·4230. Acidic hydrolysis of the methyl ether[29] gave 2-O-methyl b.p. 120° (vapour)/13 mm, n^{22} 1·4476 which was completely resistant to attack by lead tetra-acetate under the conditions described above.

Infra-red spectra. These were measured in 2 cm layers in CCl_4 solution with a 2500 l.p.i. grating used in the fourth order on the spectrometer previously described.[30] Concentration of the diol was always $<0{\cdot}005$ M; the extinction coefficients, ε, are maximum values and are equal to $(1/cl)\log_{10}(I_0/I)$ with l in cm and c in moles/litre. The results are recorded in Table 1.

[26] A. B. Foster, *Adv. Carbohydrate Chem.* **12,** 81 (1957).
[27] J. M. Bobbitt, *Adv. Carbohydrate Chem.* **11,** 1 (1956).
[28] R. C. Hockett and W. S. McClenahan, *J. Amer. Chem. Soc.* **61,** 1667 (1939).
[29] H. Hibbert and N. M. Carter, *J. Amer. Chem. Soc.* **50,** 3120 (1928).
[30] H. Spedding and D. H. Whiffen, *Proc. Roy. Soc.* A **238,** 245 (1956).

Tetrahedron, 1958, Vol. 4, pp. 361–368. Pergamon Press Ltd., London

THE CHEMISTRY OF THE NATURAL ORDER CUPRESSALES—XXI*

CUPARENE AND CUPARENIC ACID, TWO SESQUITERPENIC COMPOUNDS WITH A NEW CARBON SKELETON

C. ENZELL AND H. ERDTMAN
Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden

(*Received* 6 *June* 1958)

Abstract—An aromatic sesquiterpene, cuparene (IV), has been isolated from *Chamaecyparis thyoides*, *Biota orientalis* and *Widdringtonia*. Cuparene gives terephthalic acid on oxidation with dilute nitric acid and (+)-camphonanic acid (III) on prolonged treatment with ozone and is therefore 1-(4-methylphenyl)-1:2:2-trimethyl*cyclo*pentane. Oxidation of cuparene with chromium trioxide gives the corresponding substituted benzoic acid, cuparenic acid (V). This acid has been found to be identical with one of the sesquiterpene acids ("acid III") previously isolated from *Widdringtonia* species and now also from *Chamaecyparis thyoides*.

EARLIER studies on the heartwood constituents of conifers belonging to the family Cupressaceae have shown the presence of a high boiling, dextrorotatory sesquiterpene fraction, "widdrene II", in the South African *Widdringtonia* species *W. dracomontana*, *W. juniperoides*, *W. Schwarzii and W. Whytei*[1] and in the East Asian *Arbor vitae*, *Biota orientalis*.[2] A similar fraction has now been obtained from the North American *Chamaecyparis thyoides*[3] and it contained, according to gas chromatographic results and spectroscopic data, about 60 per cent of an aromatic hydrocarbon. The present investigation was devoted to the isolation and structural elucidation of this aromatic compound.

The low hydrogen consumption of this high boiling fraction on hydrogenation with a palladium catalyst indicated that the ethylenic linkages present are not in the aromatic component. The non-aromatic unsaturated components can be removed after treatment with ozone at low temperature. The remaining hydrocarbon, which according to gas chromatographic examination and sorption analysis is a pure compound, has the composition $C_{15}H_{22}$. The same compound was isolated, by the same procedure from *Biota orientalis* and from a mixture of sesquiterpene fractions from the *Widdringtonia* species mentioned. (mainly from *W. juniperoides* and *W. Whytei*).

The ultra-violet and infra-red (Fig. 1) absorption spectra of the compound showed the presence of a *para*-disubstituted benzene nucleus. The mass spectrum, kindly determined by R. Ryhage, Stockholm, confirmed the molecular weight (202) and showed peaks corresponding to a benzyl fragment and to fragments formed by successive removal of 1, 3, 4, 5 . . . . carbon atoms from the parent molecule.

The presence of a *para*-disubstituted benzene nucleus was confirmed by the isolation of terephthalic acid on oxidation of the compound with dilute nitric acid.

* Part XX. *Acta Chem. Scand.* **12**, 267 (1958).
[1] H. Erdtman and B. R. Thomas, *Acta Chem. Scand.* **12**, 267 (1958).
[2] H. Erdtman and Z. Pelchowicz, *Chem. Ber.* **89**, 341 (1956).
[3] C. Enzell. To be published.

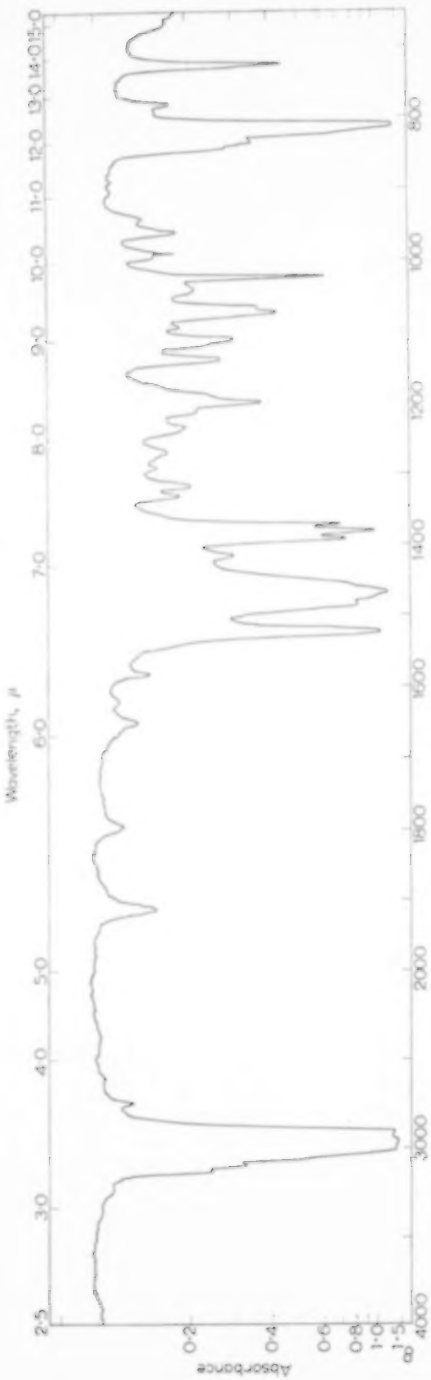
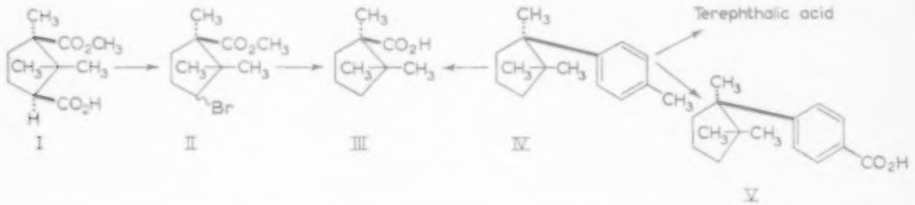


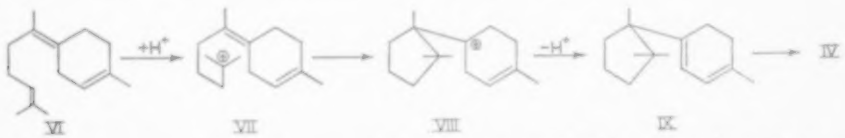
FIG. 1. Infra-red spectrum of cuparene.

Since the hydrocarbon has the composition $C_{15}H_{22}$ and does not react with ozone or hydrogen under the above conditions it must be bicyclic in agreement with the high density. Prolonged ozonisation at room temperature followed by oxidation with alkaline hydrogen peroxide furnishes an acid with the properties of (+)-camphonanic acid[4] (III) and an infra-red spectrum identical with that of (±)-camphonanic acid. The racemic acid[5] was kindly supplied by Dr. H. L. Lochte, Austin, Texas. (+)-Camphonanic acid has been obtained from (+)-camphononic acid[4] but is more conveniently prepared by a Hunsdiecker degradation of the β-monomethyl ester of (+)-camphoric acid (I) followed by reductive removal of the bromine atom and saponification of the ester. The identity of the degradation product with the synthetic specimen was established by mixed melting point, infra-red spectra and optical rotations. These degradation products account for all the carbon atoms present in the molecule and the hydrocarbon must therefore be 1-(4-methylphenyl)-1:2:2-trimethyl-*cyclo*pentane. The absolute configuration at C_1 is the same as that at the corresponding atom in (+)-camphor.[6] The name cuparene is proposed for this new sesquiterpene hydrocarbon, since it is aromatic and apparently occurs widely in the Cupressaceae.



In the communication on the *Widdringtonia* genus Erdtman and Thomas[1] reported the presence of a *para*-substituted benzoic acid, "acid III". This acid has now also been found in *Chamaecyparis thyoides*[3] and it appears highly probable that it is related to cuparene. Oxidation of cuparene with chromium trioxide in acetic acid gives an acid, which is shown to be identical with "acid III", by mixed melting point, infra-red spectra (Fig. 2) and optical rotations. The name cuparenic acid is now proposed for this compound (V).

The novel type of sesquiterpene carbon skeleton found in cuparene and cuparenic acid obeys the farnesol rule and may have a biogenetic relationship to γ-bisabolene (VI) as indicated in formulae VI–IX. (Compare also ref. 7)



The only aromatic sesquiterpene hydrocarbons previously reported are the α-curcumenes, which occur in *Curcuma aromatica* together with their dihydroderivatives, the β-curcumenes.[8] Dihydrocuparenes, *e.g.* (IX) might similarly be expected to occur

[4] H. Appel, *Z. physiol. Chem.* **218**, 202 (1933).
[5] K. Hancock and H. L. Lochte, *J. Amer. Chem. Soc.* **61**, 2448 (1939).
[6] W. Klyne, *Progress in Stereochemistry* Vol. 1, p. 189. Butterworths Scientific Publications, London (1954).
[7] L. Ruzicka, *Experientia* **9**, 357 (1953).
[8] J. Simonsen and D. H. R. Barton, *The Terpenes* (2nd Ed.) Vol. III, p. 18. Cambridge (1951); J. Simonsen and W. C. J. Ross, *The Terpenes* Vol. V, p. 514. Cambridge (1957).

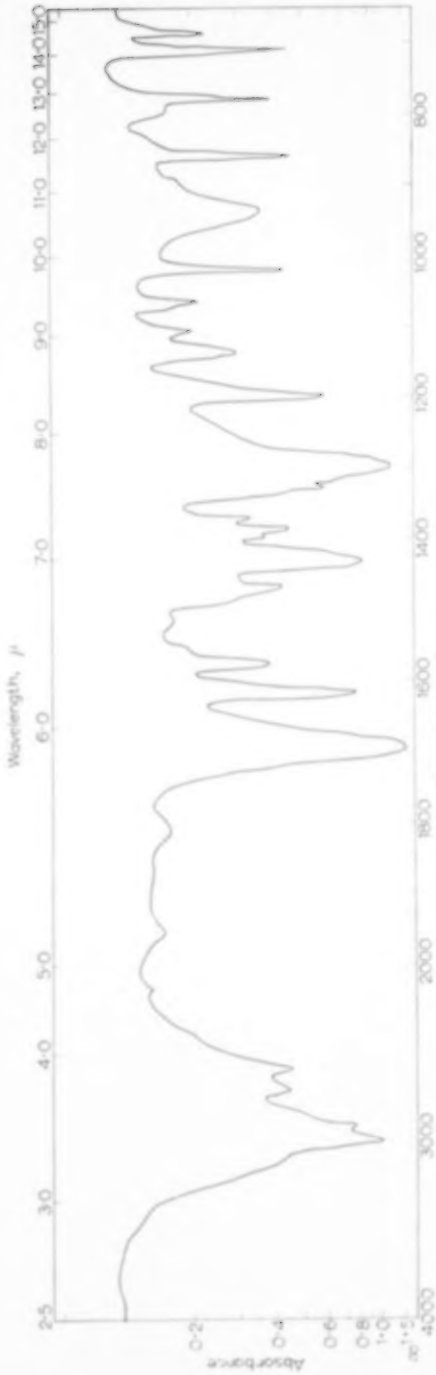


FIG. 2. Infra-red spectrum of cuparenic acid.

associated with cuparene, but attempts to isolate cuparene from the selenium dehydrogenation products of the lower boiling sesquiterpene fractions of *Chamaecyparis thyoides* and *Biota orientalis* failed, although cuparene is stable under the conditions employed.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage, unless otherwise stated. The infra-red spectra were recorded on a Perkin–Elmer No. 21 instrument (NaCl-prism; solids, KBr-disks; liquids, pure oils in 0·025 mm NaCl-cell). The ultra-violet spectra were measured in absolute ethanol on a Beckman DU spectrophotometer. Light petroleum refers to a fraction b.p. 35–60°. Microanalyses by Dr. A. Bernhardt, Mülheim.

Isolation of the fractions containing cuparene from the neutral oil of Chamaecyparis thyoides.[8] The main part (85%) of the neutral oil (3·5% air dry wood basis) from the heart-wood extract of *Chamaecyparis thyoides*, after a quick preliminary distillation, was fractionally distilled through a vacuum jacketed, packed column. Pressure 50 mm; back pressure 10 mm; reflux ratio 30 : 1. In the section of the distillation data given, temperatures were taken at the end of each fraction and the rotations were measured in chloroform.

Fraction *a*, b.p. 170°, 23·8 g, $[\alpha]_D$ +12°, n_D^{25} 1·5098; *b*, 171°, 6·4 g, +41°, 1·5121; *c*, 171°, 5·1 g, +53°, 1·5135; *d*, 173°, 11·0 g, +51°, 1·5142; *e*, 183°, 4·9 g, +53°, 1·5126.

Investigation of fraction d. This showed two strong aromatic bands (1518 and 813 cm^{-1}) in the infra-red and two absorption maxima (265, 272 mμ) in the ultra-violet. A comparison with the similar spectra of *p-tert.*-butyltoluene indicated the presence of approximately 60 per cent aromatic material.

Gas chromatographic examination of fraction *d* was made with a Perkin–Elmer vapour fractometer model 154 B. (Two metre column; 2:4-dinitrophenyl-2-naphthyl ether (20%) on celite[9]; column temp. 162°; flow rate 50 ml/min of helium; charge 5 μl). Two peaks were found with elution times 19 and 27 min. The area of the latter was about 60 per cent of the total.

Fraction *d* (1·23 g) was hydrogenated in ethanol solution (20 ml) in the presence of a palladium on charcoal catalyst (10%, 70 mg) at room temperature and atmospheric pressure. Hydrogenation ceased after 54 ml (0·37 mole, calculated for $C_{15}H_{21}$) of hydrogen had been absorbed in 10 hr.

Isolation of cuparene from Chamaecyparis thyoides. Fraction *d* (1·3 g) dissolved in methylene chloride (12 ml) was ozonised at −70° until excess ozone was present. The solvent was evaporated under reduced pressure and the product refluxed with hydrogen peroxide (30%, 2 ml) and aqueous potassium hydroxide (10%, 10 ml) for 30 min. The mixture was steam distilled and the ether extract of the distillate dried (Na_2SO_4) and concentrated. The residue was dissolved in light petroleum and filtered through alumina (100 g). Distillation of the concentrated eluate gave pure cuparene (0·7 g), b.p. 138°/19 mm, d_{21}^{21} 0·9374, n_D^{25} 1·5202, $[\alpha]_D$ +65·3° (pure oil), +65° ($CHCl_3$, *c*, 5·9), $[R_L]_D$ found: 65·9, calculated 65·7 (Found: C, 89·1; H, 11·2. $C_{15}H_{22}$ requires C, 89·0; H, 11·0%).

The higher boiling fraction (2·4 g) of fraction *a* and fractions *b–e* were all treated

[9] A. B. Groth, *Svensk Papperstidn.* **61**, 311 (1958).

in the same way. The amount of cuparene obtained was 13 g or 0·14 per cent of the air-dry wood.

Isolation of cuparene from the sesquiterpene fractions of Biota orientalis and Widdringtonia oils. A sesquiterpene fraction (b.p. 123°/10 mm, 9 g) had previously been obtained in this laboratory from the heartwood of *Biota orientalis*.[1] This, after purification as described, gave cuparene (3·5 g or 0·1 % of the air-dried wood), identified by its infra-red spectrum and physical constants.

Fractional distillation of an available sesquiterpene fraction (120 g) from the heartwoods of several *Widdringtonia* species[2] (mainly *W. juniperoides* and *W. whytei*) gave a high boiling fraction. (b.p. 138–141°/18 mm, 10 g) This, after purification as above, gave cuparene (4 g), identified by its infra-red spectrum and physical constants. An approximate calculation on the basis of the data given for the "widdrene II"-fractions in the communication on the *Widdringtonia* genus[2] gave the following percentages (air-dried wood basis) of cuparene in the different species: *W. dracomontana* (present), *W. juniperoides* (0·5 %), *W. Schwarzii* (0·1 %), *W. Whytei* (0·1 %).

Sorption analysis of cuparene (Blohm[10]) gave the following results. Sample n_D^{25} 1·5199. Fractions as removed from the silica gel column: (1) n_D^{25} 1·5202, (2) n_D^{25} 1·5202, (3) n_D^{25} 1·5202, (4) n_D^{25} 1·5202, (5) n_D^{25} 1·5199, (6) n_D^{25} 1·5142.

Gas chromatographic examination of cuparene under the same conditions as before showed only one peak (elution time 27 min).

The ultra-violet absorption spectrum of cuparene, λ_{max} 259 mμ (ε 260), 265 mμ (ε 360), 273 mμ (ε 350), cf. *p-tert.*-butyltoluene, λ_{max} 259 mμ (ε 270), 264 mμ (ε 360), 272 mμ (ε 330).

The mass spectrum was recorded on an instrument with an all-glass, heated inlet system.[11] Major peaks at m/e = 203 (5), 202 (20), 187 (4), 159 (6), 146 (8), 145 (30), 133 (14, bt), 132 (100), 131 (44), 130 (6), 129 (10). 128 (10), 120 (10), 119 (25), 117 (22, bt), 116 (7), 115 (16, bt), 105 (20, bt), 92 (5), 91 (20, bt), 83 (5), 77 (8, bt), 69 (6, cp), 65 (7, bt), 53 (4), 41 (4, bt, cp), 39 (9, bt, cp), 27 (4, bt) and 25 (4).

The figures in brackets give peak intensity as a percentage of the strongest peak (132) and show peaks in common with *p-tert.*-butyltoluene (bt) and 1:2:2-trimethyl-*cyclo*pentane (cp).[12] The peak (69) appears to be due to the five membered ring in cuparene.

Nitric acid oxidation of cuparene. Cuparene (0·5 g) and dilute nitric acid (30 %, 4 ml) were heated overnight in a sealed tube at 170°. The white crystalline material (0·3 g) obtained, was collected by filtration, washed and treated with an ethereal solution of diazomethane to give the dimethyl ester of terephthalic acid, m.p. and mixed m.p. 141–142°.

Ozonolysis of cuparene. Ozone was passed through a solution of cuparene (0·9 g) in methanol (20 ml) for 24 hr at room temperature. Most of the methanol was removed by evaporation and the residue was refluxed with a mixture of aqueous sodium hydroxide (5 %, 5 ml) and hydrogen peroxide (30 %, 1 ml) for 1 hr, cooled and extracted with ether. The alkaline solution was acidified with dilute sulphuric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and the solvent

[10] S. G. Blohm, *Ark. Kemi* **6**, 317 (1953).
[11] R. Ryhage, To be published.
[12] *Amer. Petroleum Inst. Res. Proj.* **44**, *Nat. Bur. Standards.* Catalog of Mass Spectral Data No. 443 (1949) and No. 194 (1948) resp.

removed yielding crude (+)-camphonanic acid (0,5 g), which after sublimation (80°/2 mm) and successive crystallisations from water, aq. methanol and nitromethane, melted at 191–192° (sealed tube, uncorr.), $[\alpha]_D$ + 21° ($CHCl_3$, *c*, 1·3), +17° (benzene, 1·3). (Found: C, 69·2; H, 10·3. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The toluidide melted at 116–117°. These constants agree with those given for (+)-camphoanic acid.[4] The infra-red spectrum was identical with that of (±)-camphonanic acid.

β-Methyl ester of (+)-*camphoric acid.* (+)-Camphoric acid (60 g) was esterified with diazomethane and the neutral ester (68 g) obtained was partially saponified to give the β-methyl ester[13] (42 g), m.p. 87–88°.

(+)-*Camphonanic acid.* β-Methyl hydrogen (+)-camphorate (10·7 g) was dissolved in aqueous potassium hydroxide (3·1 g, 150 ml) and a solution of silver nitrate (8·5 g) in water (50 ml) was added with stirring. The silver salt was filtered off, washed successively with water, acetone and ether and dried (80°/mm) over phosphorus pentoxide for 15 hr.

The dry silver salt (13 g) and dry carbon tetrachloride (400 ml) were placed in a three-neck flask, fitted with condenser, dropping funnel and stirrer and half the amount of solvent was distilled off. The mixture was heated under reflux and bromine (7·8 g) dissolved in dry carbon tetrachloride (30 ml) was added over a period of 30 min. The heating was continued for another 30 min and the mixture was then cooled. The silver bromide was removed by filtration and the filtrate was extracted with aqueous sodium carbonate (5%), dried (Na_2SO_4) and concentrated. A quick distillation of the remaining material gave the bromo-ester (b.p. 75–85°/0·2 mm, 5 g), which was not purified further.

Sodium (6 g) was added to a boiling solution of the bromo-ester (3 g) in absolute ethanol (200 ml) over a period of one hour. Most of the ethanol was removed by distillation and the residue, mixed with water (30 ml), was refluxed for 18 hr. The ether-extracted alkaline solution was acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated to give a semi solid product, which was dissolved in aqueous ethanol, filtered and allowed to crystallise. Colourless needles (0·4 g) were deposited which on recrystallisation and sublimation gave pure (+)-camphonanic acid, $[\alpha]_D$ + 21° ($CHCl_3$, *c*, 1·5), m.p. and mixed m.p. with the degradation product of cuparene 191–192° (sealed tube, uncorr.). The infra-red spectra of the two acids were identical.

Cuparenic acid. Cuparene (0·70 g) was dissolved in acetic acid (20 ml) and a solution of chromium trioxide (2·4 g) in acetic acid (18 ml) was added. The mixture was left at room temperature overnight and was then heated on a water-bath for 1 hr. It was poured into water (600 ml), extracted with ether and the ether extract repeatedly shaken with aqueous sodium hydroxide (10%). The alkaline solution was acidified with dilute sulphuric acid, extracted with ether and the ether extract was dried (Na_2SO_4 and concentrated to give crude cuparenic acid (0·33 g) which was purified by sublimation and crystallisation from light petroleum, m.p. and mixed m.p. with the *Widdringtonia* acid, "acid III", 158–160°, $[\alpha]_D$ +63° ($CHCl_3$, *c*, 2·4). The infra-red spectra of the two acids were identical. (Found: C, 77·8; H, 8·9; equiv. w. 235; $C_{15}H_{20}O_2$ requires C, 77·5; H, 8·7% equiv. w. 232.)

Cuparene was recovered unchanged in 80% yield after treatment with selenium at

[13] W. A. Noyes and L. R. Littleton, *J. Amer. Chem. Soc.* **35**, 78 (1913).

300° for 60 hr and in 50% yield after treatment with sulphuric acid in acetic acid (1:10) for 24 hr.

Attempts to obtain crystalline nitro-derivatives of cuparene by treatment with nitric acid or a mixture of nitric acid and sulphuric acid failed.

Acknowledgements—The authors wish to express their gratitude to Ing. R. Ryhage, Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm, for the mass spectroscopic determination, to Dr. G. Widmark, Stockholms Högskola, for the sorption analysis, to Dr. H. L. Lochte, Austin, Texas, for the sample of (±)-camphonanic acid, and to Statens Tekniska Forskningsråd for a fellowship (to C.E.).

VOL.
4
195

Tetrahedron, 1958, Vol. 4, pp. 369–381. Pergamon Press Ltd., London

MACROLIDE ANTIBIOTICS—VIII*

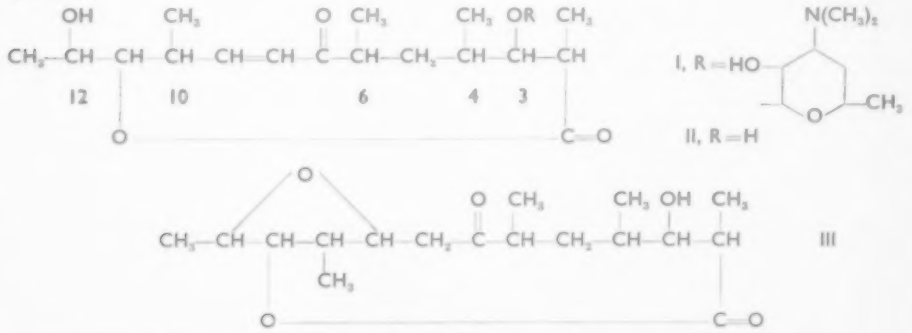
THE ABSOLUTE CONFIGURATION OF CERTAIN CENTERS IN NEOMETHYMYCIN, ERYTHROMYCIN AND RELATED ANTIBIOTICS

CARL DJERASSI, O. HALPERN, D. I. WILKINSON and E. J. EISENBRAUN
Department of Chemistry, Wayne State University, Detroit 2, Michigan, U.S.A.

(*Received* 23 *June* 1958)

Abstract—Neomethymycin (I) has been transformed into "anhydro*cyclo*neomethynolide" (V) which could be degraded *via* (−)-α-methyllevulinic acid to (−)-α-methylsuccinic acid, thus establishing the absolute configuration of positions 4 and 6 in the lactonic acid (XIII). This acid is a common degradation product of methymycin, neomethymycin, pikromycin and narbomycin and there is thus available a standard of absolute configuration for these macrolide antibiotics. By a different sequence of reactions, erythromycin (XXIII) has been converted into (+)-α-methyllevulinic acid and (+)-α-methylsuccinic acid. Coupled with earlier results reported in the literature, it is now possible to assign absolute configurations to positions 10 (R) and 8 (R) of erythromycin and this applies most likely also to positions 4 (R) and 2 (S). Attention is called to the biogenetic significance of these observations.

RECENTLY, there has been presented evidence from this laboratory[1,2] which established structure (I) for the antibiotic neomethymycin. One of the key reactions was the sulfuric acid cleavage of neomethymycin (I) to the aglycone neomethynolide (II) and the latter's internal Michael-type addition product, *cyclo*neomethynolide (III). Incidental to these studies, it was observed that when the total sulfuric acid reaction mixture was extracted with ether and the *unwashed* ether extract dried and distilled, there was produced in over 70% yield a new substance, "anhydro*cyclo*neomethynolide". The structure elucidation[3] of anhydro*cyclo*neomethynolide has opened the way to the determination of the absolute configuration of certain asymmetric centers common to several 12-membered macrolide antibiotics and the present communication deals with a description of these experiments as well as with the assignment of absolute configuration to certain centers in the 14-membered macrolide erythromycin (XXIII).



* Part VII: C. Djerassi and O. Halpern, *Tetrahedron* **3**, 255 (1958).

[1] C. Djerassi and O. Halpern, *J. Amer. Chem. Soc.* **79**, 2022 (1957).
[2] C. Djerassi and O. Halpern, *Tetrahedron* **3**, 255 (1958).
[3] C. Djerassi and O. Halpern, *J. Amer. Chem. Soc.* **79**, 3926 (1957).

The analytical composition ($C_{17}H_{26}O_4$) of anhydro*cyclo*neomethynolide indicated the loss of water as compared ($C_{17}H_{28}O_5$) to neomethynolide (II) or *cyclo*neomethynolide (III). A relationship to *cyclo*neomethynolide (III) rather than neomethynolide (II) was already indicated by the absence of the ultraviolet and infrared absorption bands associated with the latter's α:β-unsaturated carbonyl chromophore. Furthermore, it was observed that anhydro*cyclo*neomethynolide (subsequently shown to be V) could also be produced from neomethynolide (II) or *cyclo*neomethynolide (III) by solution in acidified ether followed by distillation at 40 mm. Since the ether ring of *cyclo*neomethynolide (III)—formed[2] by acid—catalysed Michael addition of the C-12 hydroxyl group of neomethynolide (II) to the double bond of the α:β-unsaturated ketone moiety—was found[2] to be quite stable, it seemed safe to assume that such an ether ring was also present in anhydro*cyclo*neomethynolide (V). In accordance with this assumption was the experimental observation that anhydro*cyclo*neomethynolide (V), just like *cyclo*neomethynolide (III), did not give any iodoform under conditions where neomethynolide (II) responded readily.

Anhydro*cyclo*neomethynolide did not exhibit any infrared hydroxyl absorption but did possess bands at 5·75 and 5·88 μ. The former was clearly due to the lactone ring and the latter was initially believed to be due to a carbonyl group until it was observed that anhydro*cyclo*neomethynolide exhibited only a positive plain* rotatory dispersion curve in contrast to the anomalous curves[2] of its three precursors I, II and III. Since the anomalous Cotton effect* curves were associated with the presence of a carbonyl group,[4] this indicated that the 5·88 μ band was due to another grouping. The most likely possibility was an enol ether function,† produced by addition of the C-3 hydroxyl group to the carbonyl group at C-7 followed by dehydration, and support for this assumption was adduced by the observation that the 5·88 μ band was not affected by reduction with lithium aluminum hydride.‡

Barring skeletal rearrangement, a cyclic ether and a cyclic enol ether grouping can be derived from neomethynolide (II) in only two ways, leading to structure (IV) or (V) for anhydro*cyclo*neomethynolide. A secure differentiation between these two alternatives seemed only possible by ozonolysis and identification of the cleavage fragments.

The ozonization was conducted at —80° in methylene dichloride, the ozonide decomposed with boiling water and the total product saponified in order to cleave the two ester linkages of the intermediate (VI). Chromatography of the resulting acid mixture on silica gel afforded two acids, the less polar of which was identified (*vide infra*) as 6-oxo-2:4-dimethyl-2-heptenoic acid (VII). No degradation experiments were performed on the more polar product, but its analysis as well as that of its ethyl ester (VIIIb) were compatible with 3:5-dimethyl-4-hydroxytetrahydrofuran-2-acetic acid (VIIIa). These two fragments could only arise from an intermediate such as (VI), from which it follows that anhydro*cyclo*neomethynolide must possess structure (V) rather than the alternative (IV).

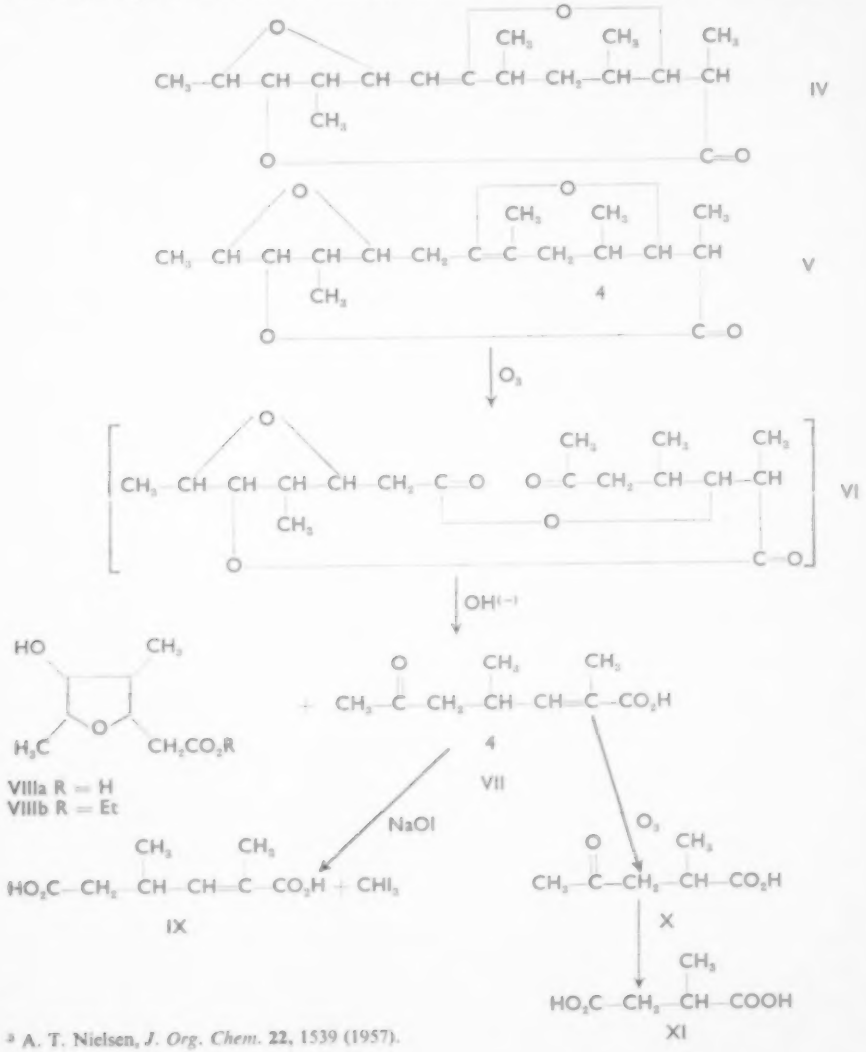
* For nomenclature in rotatory dispersion work see C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957).

† Enol ethers usually absorb in the 6 μ region [F. E. Bader, *Helv. Chim. Acta* **36**, 215 (1953)] but under certain conditions may be displaced to shorter wavelength [G. Stork, *J. Amer. Chem. Soc.* **74**, 768 (1952)].

‡ For pertinent references see J. Rudinger and M. Ferles, *Lithium Aluminum Hydride*. Czechoslovak Acad. Science, Praha (1956) and N. G. Gaylord, *Reduction with Complex Metal Hydrides*. Interscience, New York (1956).

[4] C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957).

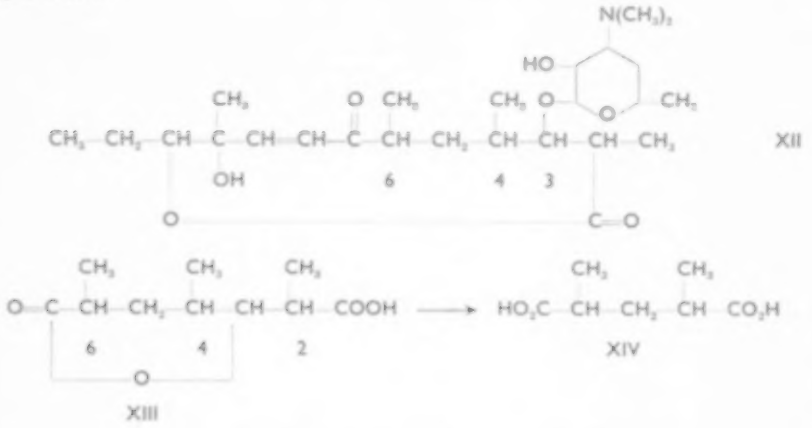
The structure of (+)-6-oxo-2:4-dimethyl-2-heptenoic acid (VII) was derived from the following considerations. The analytical composition and infrared absorption bands were consistent with formulation (VII) and the presence of a saturated carbonyl group was further demonstrated by the single, positive Cotton effect curve of this acid as well as by the formation of a yellow 2:4-dinitrophenylhydrazone. Chemical confirmation for a methyl ketone function was provided by hypoiodite oxidation of (VII) yielding iodoform and a crystalline, unsaturated dibasic acid (IX), the ultraviolet absorption[3] of which indicated that the double bond had to be in conjugation with one of the carboxyl functions. Ozonolysis of the unsaturated keto acid (VII) followed by permanganate oxidation provided (—)-α-methyllevulinic acid (X), characterized as the (+)-2:4-dinitrophenylhydrazone, and hypoiodite oxidation furnished iodoform together with (—)-α-methylsuccinic acid (XI). Since (—)-α-methylsuccinic



[3] A. T. Nielsen, *J. Org. Chem.* **22**, 1539 (1957).

acid has been related[6–8] to L-glyceraldehyde, the absolute configuration of its asymmetric center corresponds to that of C-4 in neomethymycin (I) and can be defined unambiguously as (S) according to the new convention.[9]

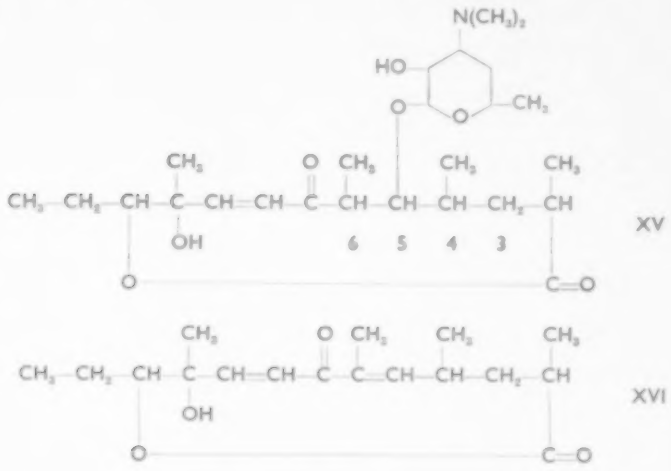
Ozonolysis[1,2] of neomethynolide (II) affords the lactonic acid (XIII) which has already been degraded[10] to *meso*-α:α′-dimethylglutaric acid (XIV). Thus with the relative configuration of C-4 and C-6 established as *cis* through (XIV), an absolute configuration of (R) can be assigned to C-6 in the structures I, II, III and XIII. Furthermore, the antibiotic methymycin (XII) has been shown[11] to differ from neomethymycin (I) only at positions 10 and 12. The steric identity of all asymmetric centers between C-1 and C-7 of neomethymycin (I) and methymycin (XII) is demonstrated by the isolation of the same lactonic acid (XIII) from both antibiotics. Consequently, C-4 and C-6 of methymycin (XII) also possess the 4S and 6R configurations.



Very pertinent to the present work is the report[10] that pikromycin[12] and narbomycin[13] also yield the same (+)-lactonic acid (XIII) upon oxidation. This observation establishes the carbon skeleton of these two antibiotics between C-1 and C-7 but does *not* prove the position of the desosamine-bearing hydroxyl group which could be at C-3 (see I and XII) or at C-5 (*e.g.* XV). Indeed, pikromycin,[12] which is isomeric with neomethymycin (I)[1,2] and methymycin (XII),[11] has been assigned[14–16] tentatively structure (XV) with the glycosidic linkage at C-5, since acid hydrolysis leads to kromycin (XVI), whose constitution is established.[15] It was pointed out,[14] however, that kromycin (XVI) could also have arisen from a structure such as (XII) by assuming

[6] A. Fredga, *Arkiv. Kemi. Min. Geol.* **24A**, No. 32 (1947).
[7] J. A. Mills and W. Klyne in W. Klyne's, *Progress in Stereochemistry* Vol. I, p. 203. Academic Press New York (1954).
[8] E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.* **77**, 3383 (1955).
[9] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).
[10] R. Anliker, D. Dvornik, K. Gubler, H. Heusser and V. Prelog, *Helv. Chim. Acta* **39**, 1785 (1956).
[11] C. Djerassi and J. A. Zderic, *J. Amer. Chem. Soc.* **78**, 2907, 6390 (1956).
[12] H. Brockmann and W. Henkel, *Chem. Ber.* **84**, 284 (1951).
[13] R. Corbaz, L. Ettlinger, E. Gaumann, W. Keller, P. Kradolfer, E. Kyburz, L. Neipp, V. Prelog, R. Reusser and H. Zahner, *Helv. Chim. Acta* **38**, 935 (1955).
[14] R. Anliker and K. Gubler, *Helv. Chim. Acta* **40**, 119 (1957).
[15] R. Anliker and K. Gubler, *Helv. Chim. Acta* **40**, 1768 (1957).
[16] H. Brockmann and R. Oster, *Chem. Ber.* **90**, 605 (1957).

a *trans*-annular hydride shift in the medium-sized 12-membered lactone ring. If pikromycin possesses the structure (XII) already proved[11] for methymycin, then the two antibiotics would differ in the stereochemistry at C-3,* which would be responsible for the ease of elimination of the hydroxyl group of pikromycin and the stability of that of methymycin in the acid cleavage of the respective antibiotics.



XV

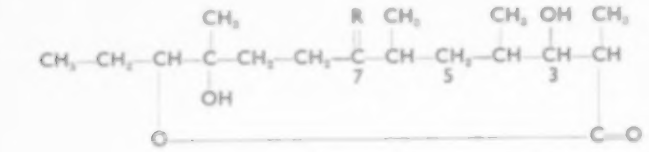
XVI

In an attempt to interconvert methymycin and pikromycin through a common intermediate, advantage was taken of the observation of Anliker and Gubler[15] that tetrahydropikronolide (XVIII or XX, depending upon whether pikromycin is XII or XV) upon oxidation with chromium trioxide in acetone solution leads to an acetonide in which the original glycosidically-bound hydroxyl group has been converted into a ketone (XXI or XXII). Consequently if, pikromycin and methymycin are simply epimeric at C-3, it might be possible to convert both antibiotics to the same acetonide-ketone (XXI). When dihydromethynolide (XVII)[11] was reduced with sodium borohydride and the resulting tetrahydromethynolide (XVIII) oxidized† under the conditions employed by Anliker and Gubler[15] with tetrahydropikronolide, there was isolated in good yield the known[11] spiroketal (XIX) rather than any ketonic acetonide, demonstrating that in the tetrahydromethynolide series (XVIII) oxidation occurs first at C-7 followed by immediate ring closure to the spiroketal (XIX) in the acid oxidation medium.

This failure at interconversion can be ascribed to three alternatives: (a) pikromycin possesses structure (XV) rather than (XII); (b) pikromycin possesses structure (XII) but isomerization at C-3 imposes on the molecule a completely different conformation with consequent differing behavior in the oxidation; (c) a difference in conformation—assuming that pikromycin and methymycin are epimeric at C-3—might also result in an alternate steric course in the sodium borohydride reduction of dihydromethynolide (XVII) and hence tetrahydromethynolide and tetrahydropikronolide, though both possessing structure (XVIII), may differ in the stereochemistry at C-7 and C-3.

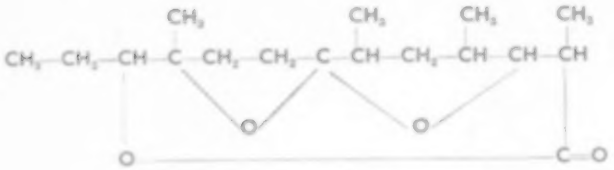
*And conceivably also at C-10 and C-11.
† Unpublished experiment by Dr. Michael Cais in this laboratory.

Such a difference at C-3 and C-7 could alter the confirmation of the medium-sized lactone ring to such an extent that the oxidation of the two epimers might proceed in completely different directions.

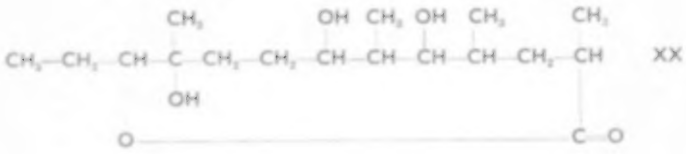


XVII R = O

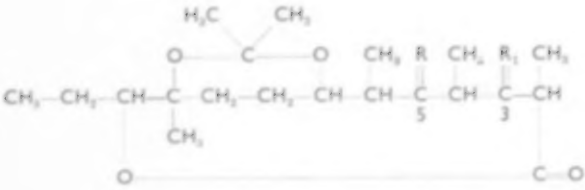
XVIII R = (OH, H)



XIX



XX



XXI R_1 = O: R = H_2

XXII R_1 = H_2: R = O

The important conclusion to be drawn is that if pikromycin does indeed possess structure (XV), carbon atoms 4 and 6 must correspond to C-4 and C-2 of the common degradation product (XIII). Since the same enantiomorph of the lactonic acid (XIII) was obtained from both methymycin (XII) and pikromycin (XV), the latter must have the opposite configuration (R) at C-4 as compared to methymycin (XII) and neomethymycin (I). In fact, the considerable likeliness exists that this antipodal relationship applies also to the other two asymmetric centers (C-2 and C-6) of these two groups of antibiotics which are represented in the common degradation product (XIII). Further discussion as to the possible biogenetic significance of this stereochemical point will be deferred until the end of this paper, but it is obvious that a definite assignment of absolute configuration to pikromycin will have to await unambiguous location of the sugar portion, a statement which applies with equal force to narbomycin.[13] Once this structural point has been settled, then an assignment of absolute configuration can be made immediately to pikromycin and narbomycin—in the manner done above for neomethymycin (I) and methymycin (XII)—since the absolute configuration of the lactonic acid (XIII) at positions 4 and 6 has been settled rigorously in the present investigation.

From a therapeutic standpoint, the most important member of the macrolide group* of antibiotics is erythromycin, whose structure (XXIII) has been elucidated in a series of outstanding investigations emanating from the Lilly Laboratories.[17,18] The same group[17] also assigned tentatively absolute configurations‡ to several asymmetric centers of erythromycin (XXIII) by the use of rotational rules, which however suffer from an inherent degree of uncertainty.† Consequently, it was felt essential to confirm these assignments as far as possible by classical chemical correlations leading eventually to L- or D-glyceraldehyde and this has now been possible through the kind co-operation of Dr. K. Gerzon and his colleagues of the Eli Lilly Research Laboratories.[17]

The multi-step conversion of erythromycin (XXIII) to the unsaturated dilactone (XXIV) has already been recorded.[18] The latter still retains carbon atoms 4, 6 and 8 of the parent antibiotic and as has already been recognised by the Lilly group,[18] this substance represents a nearly ideal substrate for the establishment, by chemical means, of the absolute configuration of one or more centers. In fact, by carrying out substantially the earlier recorded[18] degradations, except that we employed milder and non-racemizing conditions, it was possible to transform the derived saturated lactone (XXV)[18] into the required reference compound, α-methylsuccinic acid.

In order to establish that the C-8 center of the lactone (XXV) is unaffected by mild basic conditions required to open the ring, a specimen was warmed with sodium bicarbonate solution for a few minutes which was shown to result in lactone opening to the extent of over 80%. Acidification of the solution regenerated the lactone (XXV) with unchanged rotation. The reaction was now repeated on a larger scale and the solution of the dibasic acid (XXVI) was oxidised with potassium metaperiodate and the oxidation mixture treated with 2:4-dinitrophenylhydrazine. After two recrystallizations, there was obtained pure (—)-α-methyllevulinic acid 2:4-dinitrophenylhydrazone corresponding to (+)-α-methyllevulinic acid (XXVII). Comparison was effected with a sample of synthetic material which was resolved by the earlier recorded procedure[18] except that a product of considerably superior optical purity was obtained. As indicated already above in the degradation of (—)-α-methyllevulinic acid to (—)-α-methylsuccinic acid, the sign of rotation does not change in these two acids and, therefore C-8 of erythromycin corresponds to the asymmetric center of (+)-α-methyllevulinic acid, which in turn is related *via* (+)-α-methylsuccinic acid to D-glyceraldehyde. According to the new convention,[8] C-8 of erythromycin (XXIII) has the (R) configuration.‡

Gerzon *et al.*[17] have shown definitely that C-8 and C-10 of erythromycin (XXIII) must possess the opposite stereochemistry since these two centers are contained in the degradation product (—)-2:4-dimethylpentane-1:3:5-triol, which was still optically

* This term—suggested by R. B. Woodward, *Festschrift Arthur Stoll* pp. 524–544. Birkhäuser, Basel (1957).—encompasses a group of antibiotics possessing a medium-sized or large-sized lactone ring.

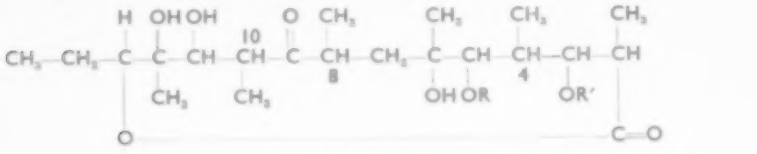
† See footnote 21 in ref. 17.

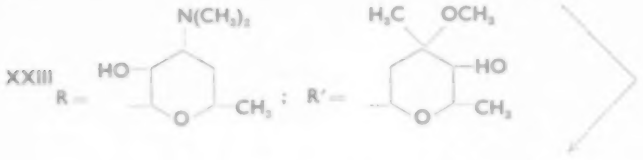
‡ Gerzon *et al.*[17]—using the system of W. Klyne, *Chem. & Ind.* 1022 (1951)—have proposed the 2L, 3D, 4L, 8L, 9D, 10D configurations. The R and S notations[8] employed in our present paper (2S, 4R, 8R, 10R) do not alter the conclusions of Gerzon *et al.*

[17] K. Gerzon, E. H. Flynn, M. V. Sigal, P. F. Wiley, R. Monahan and U. C. Quarck, *J. Amer. Chem. Soc.* **78**, 6396 (1956).

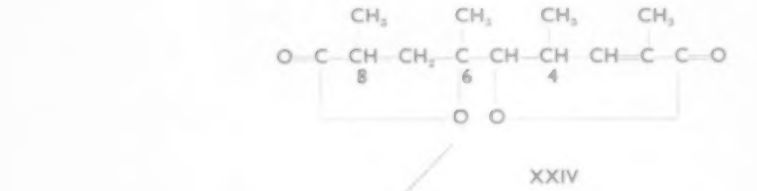
[18] P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, O. Weaver, U. C. Quarck, R. R. Chauvette and R. Monahan, *J. Amer. Chem. Soc.* **79**, 6062 (1957).

active.* Since C-8 has been shown above to possess the (R) configuration, C-10 must be assigned the (R) notation (see footnote 18 on p. 375). By means of the hydrazide rotation rule,[19] Gerzon *et al.*[17] have presented strong circumstantial evidence that the configurations of C-8 and C-4 are identical. Consequently, if one accepts the (R) configuration for C-4, it follows* that C-2 must be (S).

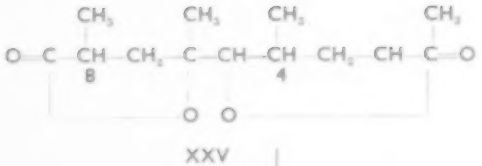




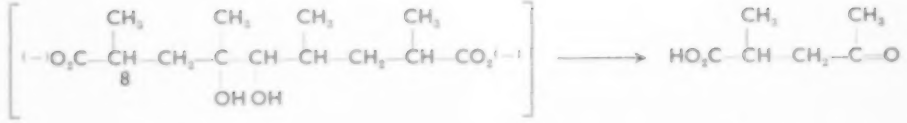
XXIII



XXIV



XXV



XXVI XXVII

The present chemical degradations have fully substantiated the earlier work[17] based on rotation rules, where it was pointed out that erythromycin (XXIII) has a "meso" character, the asymmetric centers between C-1 and C-8 possessing largely or exclusively the opposite configuration from those between C-10 and C-13 (see footnote‡ on p. 375). If one couples this observation with the possibility noted above that the C-1 to C-7 portions of neomethymycin (I) and pikromycin (XV) may be largely or

* Its *meso* isomer, on the other hand, was derived from the first five carbon atoms of erythromycin (XXIII) showing that C-2 and C-4 had to be assigned opposite (4R:2S) notations.

[19] P. Levene, *J. Biol. Chem.* **23**, 145 (1915).

exclusively enantiomeric, then one is led to the interesting speculation that biogenetically the macrolide rings* may be constructed from two fragments joined together at a late stage rather than by successive fusions of C_2 or C_3 units. Extensive biochemical experimentation with labeled precursors would be necessary to establish this intriguing point of detail.

EXPERIMENTAL†

*Anhydro*cyclo*neomethynolide* (V). A solution of 8·0 g of neomethymycin (I) methylene dichloride solvate[2] was boiled for 10 min with 400 cc of 5 N H_2SO_4, cooled, saturated with ammonium sulfate and extracted with ether. The unwashed ether solution was dried over sodium sulfate, concentrated, seeded with neomethynolide (II) and chilled. After filtering 0·825 g of neomethynolide (II),[2] the remaining ether was evaporated and the residue was distilled at a bath temperature of 180–200° and 40 mm. The entire, colorless distillate (3·3 g) crystallized and after recrystallization from aqueous acetone or aqueous methanol afforded flat prisms, m.p.168–170°, $[\alpha]_D$ +134° (chloroform), $[\alpha]_D$ +124·5° (dioxane), positive, plain dispersion curve rising to 780° at 270 mμ, $\lambda_{max}^{CHCl_3}$ 5·75 and 5·88 μ. The substance did not give any iodoform when treated with sodium hypoiodite under standard conditions[2] and did not exhibit any ultraviolet absorption maximum except for end absorption (log ε 3·78 at 220 mμ). Treatment of a small sample with lithium aluminum hydride in ether solution (24 hr refluxing) followed by decomposition with sodium sulfate yielded an oil which exhibited no more absorption at 5·75 μ but still retained the infrared band at 5·88 μ attributed to the enol ether. (Found: C, 69·15; H, 9·03; O, 22·22; C—CH_3, 23·84; OCH_3, 0·0; Calc. for $C_{17}H_{26}O_4$: C, 69·36; H, 8·90; O, 21·74; 5 C—CH_3, 25·52%).

When an ethereal solution of neomethynolide (II)[2] or *cyclo*neomethynolide (III)[2] was shaken with 5 N H_2SO_4, dried, evaporated and heated at 40 mm, there sublimed near 150° anhydro*cyclo*neomethynolide (V) in nearly quantitative yield.

*Ozonolysis of anhydro*cyclo*neomethynolide* (V). Ozone was passed for 45 min at −80° through a solution of anhydro*cyclo*neomethynolide (V, 2·0 g) in methylene dichloride (25 cc), the solution turning blue after about 35 min. The solvent was removed *in vacuo* at room temperature, the residue was heated under reflux for 1 hr with water (50 cc), followed by the addition of sodium hydroxide (10 g) dissolved in aqueous methanol (50 cc, 50%). After heating for another hour while distilling most of the methanol, the dark orange solution was cooled, saturated with sodium chloride and extracted with ether. The ether extract was concentrated to near dryness, dissolved in methanol (5 cc) and again heated under reflux (30 min) with sodium

* At the present time, this very circumstantial evidence applies only to those macrolide antibiotics which follow partially or wholly the "propionate pattern" (see reference 17). A. J. Birch in L. Zechmeister's, *Progress in the Chemistry of Organic Natural Products* Vol. XIV, p. 202. Springer, Vienna (1957); and A. J. Birch, R. J. English, R. A. Massy-Westropp, M. Slaytor and H. Smith, *J. Chem. Soc.* 365 (1958) has suggested that the extra methyl groups, which confer the "propionate pattern" upon these antibiotics, do not arise from the incorporation of biochemical equivalents of propionic acid but rather that the fundamental chain is constructed by the standard acetic acid scheme starting from acetate followed by introduction of the methyl groups from C_1 precursors. If the latter scheme obtains then it would be interesting to determine whether the unusual stereochemical features discussed above are somehow associated with this secondary methyl introduction step.

† Melting points were determined on the Kofler block. The microanalyses were performed in part by Mr. Joseph F. Alicino (Squibb Institute for Medical Research) and in part by the microanalytical staff of Eli Lilly and Co., where all X-ray diffraction patterns were obtained. We are greatly indebted to both groups for their valuable help.

hydroxide (5 cc, 10%), saturated with sodium chloride and ether extracted. The aqueous layers remaining from both ether extractions were combined, acidified with hydrochloric acid and the pale yellow solution was extracted continuously overnight with ether.

Evaporation of the dried ether solution and maintaining the residue (2·0 g of colored oil) for 30 min at 105° and 0·005 mm afforded 354 mg of a clear oil (VII). The non-volatile residue was dissolved in benzene solution and chromatographed on silica gel (100 g). Elution with benzene and benzene–ether (9 : 1) did not remove any material but when benzene–ether (7 : 3) was employed, a clear oil was obtained which was distilled at 105° and 0·005 mm; yield 231 mg (total yield 585 mg, 51%). The analytical sample of (+)-6-*oxo*-2:4-*dimethyl*-2-*heptenoic acid* (VII) was redistilled at 100° and 0·001 mm, $[\alpha]_D$ +46° (chloroform), single positive Cotton effect in dioxane (*c*, 0·123: $[\alpha]_{700}$ +18°, $[\alpha]_{589}$ +30°, $[\alpha]_{315}$ +560°, $[\alpha]_{277\cdot5}$ −1180°; the infrared absorption spectrum (chloroform solution) showed the broad band in the 3–3·5 μ region typical of acids as well as bands at 5·80, 5·88 and 6·02 μ (m). (Found: C, 62·96; H, 8·37; Calc. for $C_9H_{14}O_3$: C, 63·51; H, 8·29%).

The bright yellow 2:4-*dinitrophenylhydrazone* of (VII) was recrystallized from aqueous methanol whereupon it exhibited m.p. 142–144°. (Found: C, 51·46; H, 5·57; N, 16·05; neut. equiv., 340. Calc. for $C_{15}H_{18}N_4O_6$: C, 51·42; H, 5·18; N, 15·99%; mol. wt., 350·3).

Further elution of the silica gel column with ether–methanol (9 : 1) afforded 3:5-*dimethyl*-4-*hydroxytetrahydrofuran*-2-*acetic acid* (VIIIa), which was distilled at 140° and 0·005 mm. (Found: C, 54·39; H, 8·30; C—CH_3, 18·31; neut. equiv., 176. Calc. for $C_8H_{14}O_4$: C, 55·16; H, 8·10; 2 C—CH_3, 17·2% mol. wt., 174·2).

Treatment of a sample of the acid (VIIIa) at room temperature for 30 min with an ethereal solution of diazoethane and distillation of the crude neutral fraction at 100° and 0·005 mm afforded the *ethyl ester* (VIIIb). (Found: C, 59·08; H, 8·87; OEt, 21·87; Calc. for $C_{10}H_{18}O_4$: C, 59·38; H, 8·97; OEt, 22·28%).

(+)-1:3-*Dimethyl*-1-*butene*-1:4-*dioic acid* (IX). To (+)-6-oxo-2:4-dimethyl-2-heptenoic acid (VII, 135 mg) in pure dioxane (1 cc) was added sodium hydroxide solution (1 cc, 10%) followed by the dropwise addition of a solution of potassium iodide (2 g) and iodine (1 g) in water (8 cc) until a brown color persisted. After warming at 60° for 2 min, the mixture was decolorized by the addition of a few drops of 10 per cent sodium hydroxide and the iodoform was precipitated by addition of water (5 cc). The iodoform was collected, the filtrate was saturated with sodium chloride and extracted continuously overnight with ether (extract discarded). The aqueous solution was then acidified, a small amount of sodium bisulfite was added and the ether extraction was repeated. Evaporation of the dried ether extract and distillation at 120° and 0·001 mm yielded a clear distillate which was recrystallized twice from ether–hexane without achieving a sharp melting point. It is conceivable that the acid (IX) is a mixture of *cis* and *trans* isomers; yield, 26 mg, m.p. 130–155°, $[\alpha]_D$ +41° ($CHCl_3$), λ_{max}^{EtOH} 215 mμ, log ε 4·05. (Found: C, 55·60; H, 7·09; neut. equiv., 88; Calc. for $C_8H_{12}O_4$: C, 55·80; H, 7·03% neut. equiv. 86).

(−)-α-*Methyllevulinic acid* (X). A solution of (+)-6-oxo-2:4-dimethyl-2-heptenoic acid (VII, 80 mg) in methylene dichloride (10 cc) was ozonized at −80° until a permanent blue color was obtained (ca. 15 min). After removal of the solvent *in vacuo* and

heating of the residue for 1 hr with water (20 cc), the mixture was cooled and treated dropwise with an aqueous solution of potassium permanganate (3%) until the violet color persisted (ca. 10 min). The color was discharged with sodium bisulfite, 3 drops conc hydrochloric acid was added and after saturation with sodium chloride, the solution was extracted continuously overnight with ether. Evaporation of the solvent and distillation at 100° and 1 mm provided (−)-α-*methyllevulinic acid* (X, 19 mg) which was directly transformed into the (+)-2:4-*dinitrophenylhydrazone*. Recrystallization from aqueous methanol and from ethanol gave yellow crystals, m.p. 191–193·5° (dec),* $[\alpha]_D$ +81° (acetic acid); the infrared spectrum and the X-ray diffraction pattern were identical with those of a synthetic specimen of the antipode described below. (Found: C, 46·69, 46·05; H, 4·64, 4·75; N, 17·94; neut. equiv., 306; Calc. for $C_{12}H_{14}N_4O_6$: C, 46·45; H, 4·55; N, 18·06% mol. wt. 310·3).

(−)-α-*Methylsuccinic acid* (XI). Treatment of the total (−)-α-methyllevulinic acid obtained from the ozonolysis of (VII) with sodium hypoiodite afforded iodoform (30%) and (−)-α-methylsuccinic acid (50%), m.p. 104–105°, $[\alpha]_D$ −9° (water).

The following procedure without isolation of intermediates led to (−)-α-methylsuccinic acid (20%) based on anhydro*cyclo*neomethynolide (V): The ozonolysis was performed on anhydro*cyclo*neomethynolide (V, 600 mg), in methylene dichloride (20 cc) at −80° for 25 min, the solvent was removed and the residue was heated under reflux for 2 hr with water (25 cc). Upon cooling sodium hydroxide (1·5 g) was added, heating was continued for 1 hr, followed by the dropwise addition at room temperature of potassium iodide (4 g) and iodine (2 g) in water (16 cc). Iodoform and other neutral components were removed by ether extraction (after saturation with sodium chloride), sodium bisulfite was added to the aqueous residue which was acidified (congo red) with conc HCl and then subjected to continuous ether extraction. The residue (409 mg) after evaporation of the ether was dissolved in water (20 cc) and heated on the steam bath for 30 min with chromium trioxide (2 g) and conc sulfuric acid (5 cc). Hydrazine hydrate was added to the cooled solution until it turned blue and it was then extracted continuously overnight with ether after prior saturation with ammonium sulfate. The extract was concentrated to dryness, heated for 5 min on the steam bath with water (1 cc) again evaporated to dryness and then sublimed at 100° and 0·001 mm, furnishing (−)-α-methylsuccinic acid (26·6 mg). The residue from the sublimation was once again oxidized with chromium trioxide (1 g) in conc sulfuric acid (2·5 cc) and water (10 cc) and after repeated sublimation afforded an additional 24·7 mg (XI). Two recrystallizations from benzene–hexane raised the m.p. to 111·5–113·5°, $[\alpha]_D$ −17·5° (ethanol), the infrared spectrum and X-ray diffraction pattern being identical with a sample of the (+)-antipode derived[8] from (+)-pulegone or obtained by resolution. (Found: C, 45·32; H, 6·03; neut. equiv., 65; Calc. for $C_5H_8O_4$: C, 45·45; H, 6·10% mol. wt., 132·1.)

Resolution of dl-α-*methyllevulinic acid.* α-Methyllevulinic acid was synthesized[20] in 38% yield from ethyl α-bromopropionate and ethyl acetoacetate. The fraction with b.p. 123–129°/1·5 mm and n_D^{28} 1·4400–1·4428 was used for further work. (Found: C, 55·61; H, 7·52; neut. equiv., 129 (by electrometric titration in 66% DMF, *pKa'*, 7·3); Calc. for $C_6H_{10}O_3$: C, 55·37; H, 7·75% neut. equiv. 130.)

* In another experiment, the 2:4-dinitrophenylhydrazone exhibited m.p. 194–196° with sublimation from 165°, but this depended very much upon the rate of heating.

[20] See E. A. Braude and C. J. Timmons *J. Chem. Soc.* 3313 (1953).

The 2:4-dinitrophenylhydrazone was prepared with Brady's reagent and recrystallized from ethanol, m.p. 191–192° (dec). (Found: C, 46·36; H, 4·76; N, 18·32; Calc. for $C_{12}H_{14}N_4O_6$: C, 46·45; H, 4·55; N, 18·06%).

The resolution was performed with D-tartramidic acid hydrazide as reported earlier[18] and furnished a tartramazone with m.p. 176–177°, $[\alpha]_D^{28}$ +61·5° (*c*, 0·87 in water). This was cleaved with sulfuric acid and yielded, after continuous extraction with ether and distillation at a bath temperature of 120–140°/1 mm 51% (+)-α-*methyllevulinic acid*, $[\alpha]_D^{28}$ +11·1° (*c*, 3·9 in acetic acid). Treatment with Brady's reagent afforded the (−)-2:4-*dinitrophenylhydrazone*, m.p. 191–193° (dec) from ethanol, $[\alpha]_D^{25}$ −78·3° (*c*, 0·66 in acetic acid).

This synthetic (+)-α-methyllevulinic acid was converted into (+)-α-methylsuccinic acid in the following fashion: bromine (2·6 g) was added at 0° to a solution of sodium hydroxide (1·8 g) in water (21 cc) and this was followed by (+)-α-methyllevulinic acid (0·624 g) in water (3 cc). After stirring at room temperature for 2 hr, the mixture was let stand overnight, steam distilled for a few minutes and then extracted with chloroform (discarded). The residual aqueous solution was acidified to pH 2 with conc hydrochloric acid, saturated with sodium chloride and extracted continuously for 14 hr with ether. The ether solution was dried, evaporated and the solid residue was recrystallized from benzene–hexane to give (+)-α-*methylsuccinic acid* (103 mg), m.p. 105–106°. Two further recrystallizations from benzene raised the m.p. to 110–111°, $[\alpha]_D^{25}$ +16·5° (*c*, 0·60 in ethanol). Found: C, 45·12; H, 5·85; *pKa'* (water), 6·2 and 8·6; Calc. for $C_5H_8O_4$: C, 45·45; H, 6·10%).

Conversion of erythromycin (XXIII) *to* (+)-α-*methyllevulinic acid* (XXVII). The transformation of erythromycin (XXIII) to the saturated C_{12} lactone (XXV) has already been recorded.[18] No difficulty was encountered in repeating the reported[18] oxidation of erythralosamine[21] to the unsaturated C_{12} lactone (XXIV), m.p. 130–132°, $[\alpha]_D$ +199° (chloroform), but the yield in the hydrogenation of (XXIV, 600 mg) was raised to 88 per cent by conducting it for 1·5 hr at 23° and 756 mm with platinum oxide (150 mg) in methanol (25 cc). After trituration with *iso*propyl ether, the saturated lactone (XXV) exhibited m.p. 128–130°, $[\alpha]_D$ −71° (chloroform).

Since there existed evidence[18] that alkaline opening of the lactone (XXV) was associated with partial racemization, mild, non-racemizing conditions were examined as follows. A sample (69 mg) of the lactone was dissolved in 0·5 N Na_2CO_3 (5 cc) by warming on the steam bath for 4 min. The solution was diluted with water (60 cc) and titrated to pH 7 with standard hydrochloric acid, a blank being run simultaneously. Titration indicated formation of the dihydroxy dibasic acid (XXVI, 80%) and the solution was strongly acidified by addition of conc hydrochloric acid and left for 60 hr. Continuous extraction with chloroform for 5 hr, evaporation of the solvent and recrystallization from *iso*propyl ether provided the unchanged dilactone (XXV), m.p. and mixture m.p. 126–127°, $[\alpha]_D$ −78° (chloroform). Identity was further confirmed by coincidence of the infrared spectra.

In a preparative experiment, the dilactone (XXV, 771 mg) was dissolved in 0·5 N Na_2CO_3 (25 cc) by warming on the steam bath, the pH of the solution was adjusted to 7·6 by dropwise addition of 0·123 N HCl (11·4 cc) and potassium metaperiodate (830 mg) was added with stirring until the reagent had dissolved. After standing at

[21] E. H. Flynn, M. V. Sigal, P. F. Wiley and K. Gerzon, *J. Amer. Chem. Soc.* **76**, 3121 (1954).

room temperature overnight, the solution was acidified to pH 2 by addition of sulfuric acid (30%) and then extracted continuously with ether for 12 hr. The extract was dried and evaporated, leaving 902 mg of a light yellow oil.

A portion (592 mg) of this oil was treated with 8 cc of Brady's reagent (2 g of 2:4-dinitrophenylhydrazine, 30 cc of methanol, 10 cc of water and 4 cc of conc H_2SO_4) and after 30 min, the yellow solid (303 mg, m.p. 144–154°) was collected and recrystallized twice from ethanol. The resulting 2:4-dinitrophenylhydrazone (130 mg) exhibited m.p. 193–195°, $[\alpha]_D$ −79° (*c*, 0·92 in acetic acid) and did not give any depression in m.p. upon admixture with the above described synthetic resolved sample of the (—)-2:4-dinitrophenylhydrazone of (+)-α-methyllevulinic acid. The infrared spectrum (nujol mull) and the X-ray diffraction pattern were identical with those of the resolved material but differed significantly from those of *dl*-α-methyllevulinic acid 2:4-dinitrophenylhydrazone.

Since it has been demonstrated above with synthetic material that the (+)-antipode of α-methyllevulinic acid corresponds to (+)-α-methylsuccinic acid, the determination of the absolute configuration of C-8 and hence also of C-10 in erythromycin (XXIII) is completed.

Acknowledgments—We are deeply indebted to the Squibb Institute for Medical Research for support in the form of a fellowship and for supplies of neomethymycin as well as to Eli Lilly and Company for a generous gift of erythromycin and of erythralosamine. We should also like to express our gratitude to Dr. K. Gerzon of Eli Lilly and Co. for stimulating correspondence and to the National Heart Institute of the National Institutes of Health, U.S. Public Health Service for a research grant (grant No. H-2574).

Tetrahedron, 1958, Vol. 4, pp. 382-392. Pergamon Press Ltd., London

BICYCLANES—I

THE HALOGENATION OF 2:2:1-BI*CYCLO*HEPTANE (NORBORNANE*)

E. C. KOOYMAN and G. C. VEGTER
Koninklijke/Shell-Laboratorium, Amsterdam

(*Received* 26 *June* 1958)

Abstract—The free-radical halogenation of norbornane gives mainly the 2-halides; exo/endo ratios depending on the nature of the halogen donor. Molecular chlorine or bromine give about 70 per cent of exo- and 20–25 per cent of endo-halides: SO_2Cl_2, CCl_4, PCl_5 and $CBrCl_3$ give 95 per cent of the exo-isomer. This increased stereospecificity is ascribed to the relatively lower accessibility of the intermediate 2-norbornyl radicals from the endo-side for the bulkier reagents.

A small proportion of the 7-chloride was observed in the chlorinations with Cl_2, SO_2Cl_2 and PCl_5; the bridgehead chloride (1) could not be detected.

Competitive halogenations of norbornane and *cyclo*hexane indicate that the methylene groups in *cyclo*hexane and in the six-membered ring of norbornane are about equally reactive towards various attacking radicals.

STRAINED bicyclic compounds often display peculiar rearrangements and stereospecific reactions, which are less common with related monocyclic or strainless compounds, and it seemed of interest to investigate the behaviour of some simple bicyclanes in relation to their molecular structures.

The present paper is the first of a planned series in which the emphasis will be on "nor-compounds" rather than on their polymethylated homologues such as those occurring in many natural products, the main object being to compare the chemical behaviour of the strained bicyclic skeleton with that of related strainless systems.

2:2:1-Bi*cyclo*heptane (norbornane*) was first prepared by Komppa and Beckmann who designated it as "norbornylane". The molecule may be depicted as the boat form of *cyclo*hexane, a methylene bridge being attached to the 1 and 4 positions (A); for the purpose of illustrating chemical reactions the arrangement B is more usual:

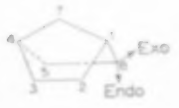


FIG. A

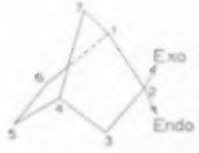


FIG. B

The geometry of the molecule is such that an appreciable strain should occur. Alder and Stein,[2] by comparison of heats of combustion of norbornane derivatives and their strainless isomers, have estimated that the strain energy should amount to

* The names norbornane and norcamphane for bi*cyclo*heptane are both used in recent papers and textbooks. Norbornane is the name accepted by the Commission on Nomenclature of the I.U.P.A.C.

[1] G. Komppa and S. Beckmann, *Ann.* **512,** 172 (1934).

[2] K. Alder and G. Stein, *Ber. Dtsch. Chem. Ges.* **67,** 613 (1934); cf. G. Becker and W. A. Roth, *Ibid.* 627. For pioneering work of Alder *et al.* see *Ann.* **504,** 228 (1933); **513,** 1, 197, 211 (1934); **525,** 183, 221 247 (1937).

about 6 kcal. Considerations of models suggest that the (3,4,5) angle and the (1,7,4) angle should be appreciably smaller than the tetrahedral value. This assumption is supported by recent findings in this laboratory.[3]

The close proximity of 2- and 6-positions in norbornane (about 2·2 Å)[3] may be related to the participation of 6-positions in solvolytic reactions involving 2-derivatives. In *cyclo*hexane, the distance between 1- and 3-positions is normal (about 2·5 Å); these effects do not occur here.[4,5]

From a standpoint of chemical reactivity norbornane has received but little attention. Gas phase nitration has been reported to give the 1-isomer in low yields.[6] Free-radical initiated chlorination has been briefly studied by Roberts *et al.* and by West and Schmerling,[8] using sulphuryl chloride and carbon tetrachloride respectively, and according to the former authors the product was 95 per cent exo-2-chloride, whereas West and Schmerling concluded that the monochlorides consisted of about 90 per cent of 2-norbornyl-chloride.

The present paper deals with free-radical initiated mono halogenations of norbornane by means of various reagents, viz. with Cl_2, CCl_4, SO_2Cl_2 and PCl_5 (chlorinations) and with Br_2, $CBrCl_3$ and N-bromosuccinimide (brominations). The mechanism involved in reactions of this type may be represented by the following scheme:

$$X\cdot + R\text{–}H\ (\text{norbornane}) \rightarrow HX + R\cdot \qquad (1)$$

$$R\cdot + Y\text{–}X \rightarrow R\text{–}Y + X\cdot \qquad (2)$$

This scheme is known to hold with the molecular halogens (X = Y = Cl or Br) as well as with CCl_4 (X = CCl_3; Y = Cl), $CBrCl_3$ (X = CCl_3; Y = Br) and N-bromosuccinimide (X = succinimidyl; Y = Br). Sulphuryl chloride reacts somewhat differently, since the SO_2Cl radical formed in (2) decomposes to form a chlorine atom and SO_2, at least in refluxing solvents, where the concentration of sulphur dioxide is low.[9] So far, the mechanism of free radical chlorinations with phosphorus pentachloride does not seem to have been investigated; this compound may react in (2) to form $PCl_4\cdot$, which then decomposes into PCl_3 and a chlorine atom continuing the chain.

1. *The halogenation of norbornane*

Conversions of norbornane were generally kept below 40 per cent in order to form mainly monohalides. Ultra-violet light, benzoyl peroxide or azo*iso*butyronitrile were used as the initiating agents. Working up was generally done by fractional distillation through an 8-plate column; after removal of hydrogen halide or chloroform and unreacted reagent, toluene was added as an entrainer to prevent clogging of the apparatus (m.p. norbornane 85°; b.p. 110°). Yields of monohalides based on halogenating agents converted (except N-bromosuccinimide) were generally high; dihalides were the only by-products detected.

[3] Personal communication, based on preliminary electron-diffraction studies, by Dr. H. Mendel of these Laboratories.
[4] J. D. Roberts, W. Bennett and R. Armstrong, *J. Amer. Chem. Soc.* **72**, 3329 (1950).
[5] S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall, *J. Amer. Chem. Soc.* **74**, 1127 (1952).
[6] R. T. Blickenstaff and H. B. Hass, *J. Amer. Chem. Soc.* **68**, 1413 (1946).
[7] J. D. Roberts, J. Urbanek and R. Armstrong, *J. Amer. Chem. Soc.* **71**, 3049 (1949).
[8] J. P. West and L. Schmerling, *J. Amer. Chem. Soc.* **72**, 3525 (1950).
[9] G. A. Russell and H. C. Brown, *J. Amer. Chem. Soc.* **77**, 4031 (1955).

The compositions of isomers in monochloride cuts (b.p. 52–53°/20 mm Hg) were determined by infra-red absorption spectrophotometry based on standard samples (the pure exo-2-chloride, 7-chloride containing some nortricyclyl chloride, a mixture containing about 70 per cent of endo- and 30 per cent of exo-2-chloride). The infra-red analyses were supported by occasional solvolysis runs, exo-2-halides being solvolysed much more rapidly than the other isomers.[4] Gas-liquid chromatography failed to resolve the monochloride cuts; only a single peak was found in check runs with samples containing exo- and endo-2-chloride as well as 7-chloride. For the determination of exo-2-bromide, the infra-red bands found for the chloride were used; endo-2-bromide was not determined directly.

TABLE 1. HALOGENATIONS OF NORBORNANE

Halogen donor	Initiator	Solvent	Temperature °C	Norbornyl chloride (%)*		
				exo-2	endo-2	7-
Cl_2	u.v. light	CH_2Cl_2	42	70 (71)	25	2
Cl_2	u.v. light	CCl_4	40–50	73	22	‡
Cl_2	None	Gas phase	150	70 (71)	25	3
SO_2Cl_2	benzoyl peroxide	CH_2Cl_2	42	95	1–5	5
CCl_4	benzoyl peroxide	CCl_4	80	95	1–5	0
PCl_5	u.v. light	CH_2Cl_2	42	95 (95)	1–5	5
PCl_5	u.v. light	CCl_4	80	95	1–5	3
PCl_5	benzoyl peroxide	Chlorobenzene	105	90	‡	‡
Br_2	u.v. light	CCl_4	80	75†	‡	‡
$CBrCl_3$	2:2′-azo*iso*butyronitrile	$CBrCl_3$	80	98 (95)	‡	‡

* The infra-red spectra gave no indications of the presence of other than 2- or 7-halides. Percentages given are based on infra-red spectra, the accuracy being probably better than 5 per cent. Values in brackets refer to percentages obtained by solvolysis.

† The remaining 25 per cent is probably endo-bromide.

‡ Not determined.

Chlorination with phosphorus pentachloride did not proceed satisfactorily when using benzoyl peroxide as the initiator at 80°. The difference between this result and successful chlorination at 105° may be due to a direct interaction of the initiator with PCl_5 without the formation of initiating radicals. Thus, at high temperatures and low peroxide concentrations, homolysis of the peroxide is sufficiently rapid to cause initiation; at the lower temperature, bi-molecular destruction of the peroxide prevails. This interpretation is supported by the fact that homolytic benzoyl peroxide decomposition is known to possess a high temperature coefficient (30 kcal) as well as by the smooth chlorinations with PCl_5 under the influence of ultra-violet light.

In the attempts to brominate norbornane with N-bromosuccinimide a dark brown colour was observed after ½ hr refluxing of the carbon tetrachloride solution. Some bromide, contaminated with bromo*iso*butyronitrile was formed, but could not be purified. It is believed that the small extent to which bromination did take place should be ascribed to free bromine formed rather than to the bromoimide. The procedure was followed which has been used by Ford and Waters for the bromination of *cyclo*hexane.[10] A single experiment carried out with *cyclo*hexane and

[10] M. C. Ford and W. A. Waters, *J. Chem. Soc.* 2240 (1952).

N-bromo-succinimide in carbon tetrachloride showed that here, too, a dark colour developed. Roberts *et al.* also failed to obtain a pure bromide when treating norbornane with the bromoimide.[11]

2. *Competitive halogenations of* cyclo*hexane and norbornane*

These reactions were run in carbon tetrachloride or methylene chloride solution. Relative amounts of monohalides were determined by gas-liquid chromatography; the results were in good agreement with those obtained by isolation of the product.

TABLE 2. COMPETITIVE HALOGENATION OF NORBORNANE AND *cyclo*HEXANE (molecular ratio 1 : 1)

Halogenating agent	Initiator	Solvent	Temperature °C	$\frac{k_{cyclohexane}}{k_{norbornane}}$ *
Cl_2	u.v. light	CCl_4	0–3	1·01 ± 0·05 (i : 1·00)
Cl_2	u.v. light	CCl_4	80	1·27 ± 0·05
SO_2Cl_2	benzoyl peroxide	CH_2Cl_2	42	1·31 ± 0·05
SO_2Cl_2	benzoyl peroxide	CCl_4	50	1·35 ± 0·05 (i : 1·33)
CCl_4	benzoyl peroxide	CCl_4	80	1·42 ± 0·05
Br_2	u.v. light	CCl_4	0–5	0·98 ± 0·05
Br_2	u.v. light	CCl_4	80	1·79 ± 0·05
$CBrCl_3$	2:2′-azo*iso*butyro-nitrile	$CBrCl_3$	80	1·44 ± 0·05 (i : 1·40)

* Mean values from 2–4 experiments (gas-liquid chromatography)
(i) Refers to values obtained by product isolation.

DISCUSSION

1. *Relative reactivities of the various positions in norbornane*

If (1) is an irreversible process under the experimental conditions, the relative amounts of halides having their halogen atom attached to a certain carbon atom provide a reliable measure for the relative reactivity of that position towards the attacking species X· in (1). This is appreciably exothermic only for the cases in which X· is a chlorine atom; the back reaction may then be neglected.

With $\cdot CCl_3$, (1) will be more nearly thermoneutral. Alkyl radicals are known to react more readily with CCl_4 or $CBrCl_3$ than with $CHCl_3$, whereas the latter is present in very low proportion, and (1) will be practically irreversible.

Only in the case of bromination with Br_2 might the back reaction have a sufficiently low activation enthalpy to compete with the forward process. The only bromides detected were the 2-halides; it would seem unlikely that the 7- or 1-norbornyl radical, once formed, should preferentially attack HBr (to regenerate norbornane) rather than Br_2. However, since no detailed study of the monobromides was made the possibility that small amounts of other bromides were present is not definitely excluded.

The occurrence of reactions of the type $R'\cdot + RH \rightarrow R'H + R\cdot$ can be neglected because of the relatively high activation enthalpies of such processes as compared with the reactions between R′· and halogen donor.

The 2-halides appear to be the main products in all cases (Table 1); only with Cl_2, SO_2Cl_2 and PCl_5 was a small proportion of the 7-halide observed. This may be due

[11] J. D. Roberts, E. R. Trumbull, W. Bennett and R. Armstrong, *J. Amer. Chem. Soc.* **72**, 3116 (1950).

to the fact that the latter chlorinations involve the highly reactive and therefore non-selective chlorine atom in (1). With CCl_4, the abstraction step proceeds by the less reactive $\cdot CCl_3$.

The lower reactivity of the 7-position compared with the 2-positions is probably related to the decreased bond angle (1, 7, 4); formation of the 7-norbornyl radical should be resisted by a further increase of angle strain. In agreement with our halogenation results, methyl radicals react more slowly with methylene groups in *cyclo*butane than with those in *cyclo*pentane or -hexane.[12]

The formation of bridgehead halides (1-chloride) could not be detected; their absence has not been definitely demonstrated, however. Here, formation of the radical would involve an appreciable increase of strain.

2. *Relative reactivities of* cyclo*hexane and norbornane*

The k_c/k_n values recorded in Table 2 may be used for a comparison of the relative reactivities of a methylene group in *cyclo*hexane and a 2-methylene group in norbornane. Since the four 2-methylene groups in the latter compound are responsible for about 95 per cent of the norbornyl halides, this comparison may be obtained multiplying k_c/k_n with $2/3 \times 1/0{\cdot}95$.

The relative reactivities thus calculated are fairly close to unity (0·7–1·3), suggesting that the two types of methylene groups have comparable reactivities. The increases of k_c/k_n at increasing temperatures indicate, however, that the reaction with norbornane involves somewhat lower activation enthalpies, viz. ½–1½ kcal, for all attacking radicals.*

There are no *a priori* reasons for assuming that the exo- and endo-hydrogens will react at exactly the same rates; it should be noted, however, that sterical accessibilities will not be much different (cf. par. 3, Fig. D). Probably, the same radical will be formed when removing either the exo- or the endo-H atom; this radical will have a planar or near-planar configuration with regard to the three remaining valencies at C-2.

The similar reactivity and only slightly lower activation enthalpy for norbornane as compared with *cyclo*hexane suggests that the 2-norbornyl radical is not appreciably stabilised by additional resonance as compared with the *cyclo*hexyl radical. A similar conclusion was arrived at by Cristol and Brindell[13] on the basis of their studies on free radical initiated addition of *p*-thiocresol to norbornene. This is in contrast to the marked stabilisation through carbon-bridging which has been established for the 2-norbornyl cation.[4,5]

3. *Exo-endo ratios*

In the preceding section the assumption was made that only a single 2-norbornyl radical is formed when removing either the exo- or the endo-hydrogen atom. Assuming that this radical has a planar or near-planar configuration at the unsaturated centre, formation of either exo- or endo-isomers then depends on (2), the halogen donor attacking *either side of the plane*. Fig. C indicates that accessibility from the

* The limited data available suggest that the lower activation enthalpies are counterbalanced by lower temperature-independent factors.

[12] A. F. Trotman-Dickenson, *Quart. Rev.* 7, 198 (1953).
[13] S. J. Cristol and G. D. Brindell, *J. Amer. Chem. Soc.* **76**, 5699 (1954).

endo-side is less than that from the exo-direction because of the shielding effect of the methylene group in the 6-position. The difference should be the more significant the bulkier the halogen donor involved.

This expectation appears to be borne out by the experimental results. Thus, the small halogen molecules give appreciable proportions of endo-isomer, whereas the other reagents yield only small percentages. The latter results are in agreement with those of Roberts *et al.*,[4] who concluded that chlorination of norbornane with sulphuryl chloride gives 95 per cent of exo-2-chloride.*

Similarly, addition of the bulky *p*-thiocresyl radical to norbornene-2 gives exclusively the exo-addition product.[13] Unfortunately, the stereochemistry of addition of "small" radicals to norbornene has not been investigated.

The fact that molecular chlorine gives the same exo-endo ratios at 0° and 80° (liquid phase) as well as at 150° (gas phase) suggests that these ratios are governed by temperature-independent factors rather than by differences in activation enthalpies in (2).

Finally, it should be noted that, in contrast to (2), the first step should hardly be affected by sterical factors because of the appreciable distance between the approaching reagent and the shielding methylene group in the 6-position (cf. Figs. C and D).

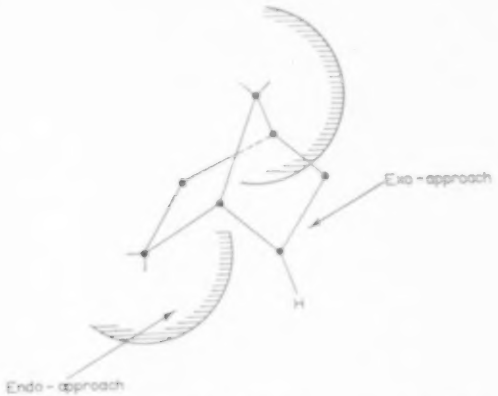


FIG. C. Shielding of endo side of 3(=2, 5 or 6)-norbornyl radical (schematically).

4. *Mechanisms of chlorination with* PCl_5

The present data may be satisfactorily explained on the basis of our proposed scheme, which is analogous to that assumed for chlorinations with sulphuryl chloride. Since only a small proportion of endo-2-chloride is observed, it seems improbable that the reaction occurs through free chlorine, which might be formed from PCl_5 by a reaction $PCl_5 \rightarrow PCl_3 + Cl_2$. The operation of the reaction $PCl_4\cdot + R{-}H \rightarrow R\cdot + PCl_3 + HCl$ cannot be excluded; however, the formation of some 7-chloride suggests that the hydrogen abstracting agent in (1) is unselective, which may favour $Cl\cdot$ rather than $PCl_4\cdot$. Chain termination may proceed by a disproportionation reaction of $PCl_4\cdot$ forming a mixture of trichloride and pentachloride.

* In a footnote to the paper by Roberts *et al.* cited above, the authors pointed out that this high degree of specificity was unusual, but no explanation was offered.

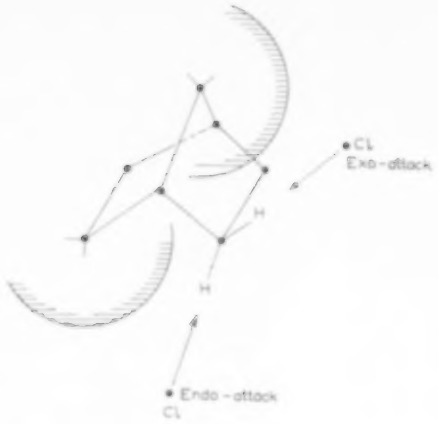


FIG. D. Illustration of minor differences in exo- or endo-attack at 3(=2 ,5 or 6)-position in norbornane (schematically).

EXPERIMENTAL

1. *Preparation of norbornane*

A steel high-pressure bomb (5 l.) was charged with freshly distilled commercial norbornadiene (450 g), b.p. 89·5°, n_D^{20} 1·4710, Ni-on-kieselguhr catalyst (23 g, 20% Ni) and hydrogen (35 atm). The bomb was set in rotation and slowly heated to 110–120° (110° after 1 hr). After 2 hr the pressure had fallen to 8 atm and the bomb was charged again with hydrogen to 60 atm. When the pressure had become constant (22 atm), the bomb was cooled, hydrogen allowed to escape and the solid contents diluted with pentane. The catalyst was removed by filtration and the filtrate shaken with sulphuric acid (96%) until the latter remained colourless. After washing with water, bicarbonate solution and again water, the pentane solution was dried over calcium chloride. Distillation yielded norbornane (347 g), b.p. 105° and m.p. 85·5–86° (lit.[1] m.p. 86–87°).

2. *Chlorination of norbornane*

(a-1) *With* Cl_2 *in solution.* Norbornane (96 g, 1 mole) dissolved in methylene chloride (80 ml) was irradiated with ultra-violet light while a slow stream of chlorine was passed in during 5 hr. The reaction mixture was distilled through an 8-plate Vigreux column. After removal of the methylene chloride, norbornane (15 g) was collected at 130°. After cooling, toluene (87 g) was added to the residue and toluene and norbornane distilled together at 145°. The combined toluene fractions were 90 g. The distillation was continued at 20 mm, and chloride (46·4 g, 35·6%) collected, at 52–53° which solidified at 5·3 to 3·1°, n_D^{20} 1·4851. (Found: Cl, 27·0; Calc. for $C_7H_{11}Cl$: Cl, 27·2%.) In the literature the following physical constants are given for the isomeric monochloronorbornanes: exo-norbornyl chloride: n_D^{20} 1·4849; m.p. −5°[14] endo-norbornyl chloride: n_D^{25} 1·4835; m.p. +28° (containing about

[14] L. Schmerling, *J. Amer. Chem. Soc.* **68**, 195 (1946).

20% of exo-isomer);[4] 7-chloronorbornane: n_D^{25} 1·4878 (containing about 15% of nortricyclyl chloride).[15]

The distillation residue amounted to 8·3 g. The amount of norbornane in the toluene fractions was determined mass-spectrometrically to be 24·6 g. Some norbornane may have been lost owing to its high volatility. The yield of monochloride based on norbornane converted and lost (56·4 g) thus amounted to about 60%.

(a-2) *With* Cl_2 *in the gas phase*. A gaseous mixture of norbornane, benzene, chlorine and nitrogen (4 : 2 : 2 : 1) was passed at 150° through a Pyrex glass tube for 1 min. Benzene did not react under these conditions. The colourless liquid reaction mixture was collected and worked up as in (a-1). From norbornane (82 g), norbornyl chloride (37·9 g, 34·0%), b.p. 52–53°/20 mm; n_D^{20} 1·4852, chlorine content 27·4%, solidifying at 6·0 to 3·9°. A higher-boiling liquid (7·7 g) was also formed.

An experiment carried out at 250° was unsuccessful owing to the deposition of carbon.

(b) *With* SO_2Cl_2. Norbornane (96 g, 1 mole) was dissolved in methylene chloride (80 ml) and SO_2Cl_2 (34 g, 0·25 mole) together with benzoyl peroxide (0·25 g, 0·001 mole) added. The mixture was refluxed for 24 hr and yielded chloride (24·6 g, 19%), b.p. 52–53°/20 mm and solidifying at −4·8 to −6°; n_D^{20} 1·4844. Norbornane (74 g) was recovered; distillation residue was 2·2 g, and yield of monochloride based on norbornane converted and lost (22 g) amounting to 83%.

(c) *With* CCl_4. Norbornane (24 g, 0·25 mole) and benzoyl peroxide (3 g, 12·5 mole) were dissolved in carbon tetrachloride (100 ml) and the solution refluxed for 24 hr, and worked up according to (a-1) gave norbornyl chloride (8 g, 24·5%) n_D^{20} 1·4845, m.p. −5 to −6°; residue (2 g); higher-boiling products did not appear to have been formed.

(d-1) *With* PCl_5. A boiling solution of PCl_5 (52·1 g, 0·25 mole) and norbornane (48 g, 0·5 mole) in carbon tetrachloride (500 ml) was irradiated with ultra-violet light. After 31 and 55 hr, respectively, 73 and 98% of hydrogen chloride had been evolved.

The phosphorus trichloride and carbon tetrachloride were distilled and the residue fractionated *in vacuo*. Norbornyl chloride (15 g, 23·0%) were collected at 52–53°/20 mm; n_D^{20} 1·4841; m.p. −5 to −6°. The residue amounted to 9·3 g.

The distillate of PCl_3 and CCl_4 was shaken with water for 3 hr, the total acid being determined by titration with alkali and chloride ion by Volhard titration. Thus PCl_3 (0·24 mole, 96%) were found in the distillate.

With the same quantities of reactants in boiling methylene chloride as the solvent, 31·4 and 89% of hydrogen chloride was evolved after 31 and 117 hr respectively, and PCl_3 (216·5 mmoles, 87%) was present in the distillate.

The yield of norbornyl chloride, n_D^{20} 1·4843, m.p. −5 to −6° was 11 g (16·9%); the residue amounted to 7 g, containing PCl_5 (28 mmoles, 11·2%).

(d-2) *With* PCl_5 *and benzoyl peroxide*. A solution of norbornane (24 g, 0·25 mole), PCl_5 (26 g, 0·125 mole) and benzoyl peroxide (1·8 g, 0·007 mole) in chlorobenzene (150 ml) was stirred and at 100–105° a smooth reaction took place. After 45 min hydrogen chloride (0·108 mole) had been evolved and the reaction was complete after 1½ hr. Phosphorus trichloride was distilled, toluene (40 ml) added and the mixture fractionated carefully. Norbornyl chloride (6·9 g, 0·053 mole, 21·2%) were collected,

[15] J. D. Roberts, F. O. Johnson and R. A. Carboni, *J. Amer. Chem. Soc.* **76**, 5692 (1954).

b.p. 84–88°/76 mm, n_D^{20} 1·4848 with a chlorine content 26·9% (calc. 27·2%) and solidifying between −5° and −10°.

3. *Bromination of norbornane*

(a) *With bromine.* To a solution of norbornane (36 g, 0·38 mole) in boiling carbon tetrachloride (100 ml), bromine (18 g, 0·11 mole) was gradually added under irradiation with ultra-violet light. At the end of the reaction, the reaction mixture was slightly yellow, and worked up in accordance with the chlorination experiments. Norbornyl bromide (12·7 g, 25·6%) was collected at 68–70°/17 mm, n_D^{20} 1·5147; and residue (2·8 g) remained. (Found: C, 48·1; H, 6·5; Br, 45·6; Calc. for $C_7H_{11}Br$: C, 48·02; H, 6·33; Br 45·7%.) In the literature the following physical constants are given for the isomeric monobromonorbornanes: exo-norbornyl bromide: b.p. 84–87°/31 mm, n_D^{25} 1·5126;[11] endo-norbornyl bromide: b.p. 70°/15 mm, n_D^{25} 1·5198.[4]

(b) *With* $CBrCl_3$ *and azoisobutyronitrile.* A solution of norbornane (12 g, 125 mmoles) and 2:2-azo*iso*butyronitrile (0·98 g, 6 mmoles) in bromotrichloromethane (105 g) was kept at 80° for 24 hr.

After removal of chloroform and bromotrichloromethane at 100 mm, the residue was cooled to −15°; a solid separated which after crystallisation from methanol, had m.p. 185–186° and mixed m.p. with hexachloroethane 186° (closed capillary).

Distillation of the residue at 20 mm afforded norbornyl bromide (5·2 g) which by mass-spectrometrical analysis was shown to contain 15% hexachloroethane. Infra-red analysis showed 84% exo-norbornyl bromide to be present.

(c) *With* N-*bromosuccinimide.* To a solution of norbornane (24 g, 0·25 mole) in carbon tetrachloride (200 ml), N-bromosuccinimide (18 g, 0·1 mol) and 2:2′-azo*iso*-butyronitrile (0·25 g, 1·5 mmoles) were added and the mixture was gently refluxed. The bromosuccinimide dissolved slowly, after 35 min a slightly yellow colour developed and succinimide precipitated. Then the colour of the reaction mixture turned to brown, possibly owing to the formation of free bromine. The brown colour subsequently changed to light yellow and after 16 hr refluxing a black deposit was present on the bottom of the reaction vessel. Distillation gave an impure bromide (3·5 g), which from its infra-red spectrum appeared to contain some bromo*iso*-butyronitrile. Pure norbornyl bromide could not be isolated; the amount of exo-isomer could not be determined in the impure product.

4. *Competitive halogenations of norbornane and* cyclo*hexane*

A solution of *cyclo*hexane (4·21 g, 50 mmoles) and norbornane (4·783 g, 50 mmoles) in carbon tetrachloride (50 ml) was boiled under reflux and a solution of chlorine (10 mmoles) in carbon tetrachloride (50 ml) was injected in the bottom of the reaction vessel under irradiation with ultra-violet light.

At the end of the reaction, the hydrogen chloride and carbon tetrachloride were removed *in vacuo* leaving a residue (20 ml). This residue was analysed by gas-liquid chromatography employing a column of dinitrodiphenic $C_5 - C_6$ ester on Sterchamol at 120° with β-ray detection in hydrogen as the carrier gas.[16] A heat conductance cell could not be used for detection owing to decomposition of the chlorides on the platinum wire and subsequent corrosion of the wire by the chlorine formed.

[16] A. I. M. Keulemans, *Gas Chromatography*. Reinhold, New York (1957).

The G.L.C. analysis showed the monochlorides to contain norbornyl chloride (45% molar) cyclohexyl chloride, (55% molar), hence,

$$\frac{k_c}{k_n} = \frac{\log\left(1 - \frac{5{\cdot}5}{50}\right)}{\log\left(1 - \frac{4{\cdot}5}{50}\right)} = 1{\cdot}27.$$

All our competition experiments were carried out in an analogous manner; sulphuryl chloride chlorinations were initiated by benzoyl peroxide, so was the chlorination by carbon tetrachloride. The bromination with bromotrichloromethane was initiated by 2:2′-azo*iso*butyronitrile. In the latter experiment the bromotrichloromethane was completely removed from the reaction mixture before G.L.C. analysis, by codistillation at 100 mm with toluene until the distillate had the refraction of pure toluene.

5. *Infra-red spectroscopic measurements*

Infra-red spectra were determined in a Grubb–Parson double beam spectrometer from 2 to 15 μ, and in a Perkin–Elmer 112 spectrometer from 15 to 25 μ.

Contents of exo-2-chloronorbornane were calculated on the basis of the spectrum of the pure exo-compound, using the absorption bands at 8·76 and 17·05 μ. Comparison of the results indicated that the latter band is most trustworthy. For the determination of exo-bromonorbornane the same absorption bands were used; with the bromonorbornanes no contents of endo-isomer were determined, only the pure exo-compound being available as a standard.

For the determination of endo-chloride contents the absorption bands at 11·56, 10·02 and 9·38 μ were used. In the standard compound, which consisted of exo- and endo-2-chloronorbornane, the amount of endo-isomer was calculated from the band at 22·12 μ.

Comparison of the spectra with that of 7-chloronorbornane showed that this isomer was present in all mixtures, except in that obtained in the benzoyl peroxide initiated chlorination with CCl_4.

The spectra of all mixtures showed absorption bands which cannot be attributed to the exo-2-, endo-2- or 7-chloride. In view of the complicated spectra and the low intensities of these bands, a definite identification was not possible.

6. *Solvolysis of norbornyl chlorides*

Solvolysis experiments according to the method of Brown and Fletcher[17] were carried out in 70% aqueous ethanol at 70°. Since the solvolysis rates of endo-2- and 7-chloronorbornane are very low as compared with that of the exo-2-chloride,[4,15] the amount of the exo-isomer could be calculated from a plot of log $(a-x)$ against time.

At 70°, for the pure exo-2-chloride a first-order rate constant $3{\cdot}4^7 \times 10^{-5}$ sec^{-1} was found up to a conversion of over 98%; the first-order constant for the endo-chloride, derived from the last part of the solvolysis plot of a 75 : 25 mixture of endo- and exo-chloride, was found to be $2{\cdot}5 \times 10^{-7}$ sec^{-1}.

[17] H. C. Brown and R. S. Fletcher, *J. Amer. Chem. Soc.* **71**, 1845 (1949).

In all cases the data obtained in solvolysis experiments agreed very well with the results of infra-red measurements.

7. *Preparation of standard compounds for infra-red spectroscopic measurements and solvolysis*

(a) *Exo-2-chloronorbornane* was prepared according to Schmerling,[14] by addition of HCl to norbornene. After working-up by fractional distillation pure exo-2-chloride (87%) was obtained, b.p. 55·5°/21 mm, m.p. −5°, n_D^{20} 1·4844. The solvolysis of this product at 70° in ethanol (70%) proceeded by a first-order reaction to over 98%, with $k_1 = 3{\cdot}4^7 \times 10^{-5}$ sec^{-1} from the chloride (8·16 mmoles) HCl (8·15 mmoles) were formed.

(b) *Exo-2-bromonorbornane* was prepared according to Roberts *et al.*[11] by addition of HBr to norbornene. The yield of the crude 2-bromonorbornane, b.p. 84–87°/31 mm, was 77%. Fractional distillation in a 35 cm Vigreux column gave pure exo-2-bromonorbornane (72%) b.p. 82°/29 mm, n_D^{25} 1·5126, d_D^{25} 1·3808.

(c) *Endo-2-chloronorbornane*. Diels–Alder addition of vinyl chloride to *cyclo*pentadiene and subsequent catalytic hydrogenation gave a norbornyl chloride which consisted of endo-2-chloride (60%) and exo-2-chloride (40%), according to infra-red spectroscopic analysis in comparison with the pure exo-compound.

The above chloride (10 g) were refluxed for 16 hr in a solution of Na_2CO_3 (2g) in water (20 ml) and acetone (25 ml). After addition of more water, ether extraction and drying and evaporation of the ether, the semi-solid residue was percolated over silica with pentane elution. Evaporation of the pentane and fractional distillation gave monochloride (3·4 g) b.p. 79°/48 mm, m.p. 30·1–30·5°.

Solvolysis of the above compound according to Brown and Fletcher[17] showed it to consist of 73% endo- and 27% exo-isomer. This was confirmed by infra-red spectroscopic analysis, which indicated the presence of 25–30% exo-compound.

(d) *7-chloronorbornane* was synthesised according to Roberts *et al.*[15] by pyrolsis of *syn*-7-chloro-exo-norbornyl-2-naphthoate and catalytic hydrogenation of the resulting *syn*-7-chloronorbornene. On fractional distillation, two fractions with b.p. 91°/8·5 mm were obtained; the first, 0·7 g, n_D^{20} 1·4827, was partly solid at room temperature; the second, 1·0 g, n_D^{20} 1·4866, solidified at about 0°. The latter fraction was used as a standard compound in spectroscopic measurements; its infra-red spectrum agreed with that given by Roberts, showing that it also contained 15–20% of nortricyclyl chloride.

Tetrahedron, 1958, Vol. 4, pp. 393–402. Pergamon Press Ltd., London

STEREOCHEMISTRY OF THE HALOLACTONISATION REACTION

THE REACTION OF *CIS*- AND *TRANS*- STILBENE-2-CARBOXYLIC ACIDS WITH HALOGENS

G. BERTI
Institute of Pharmaceutical Chemistry University of Pisa

(*Received* 26 *June* 1958)

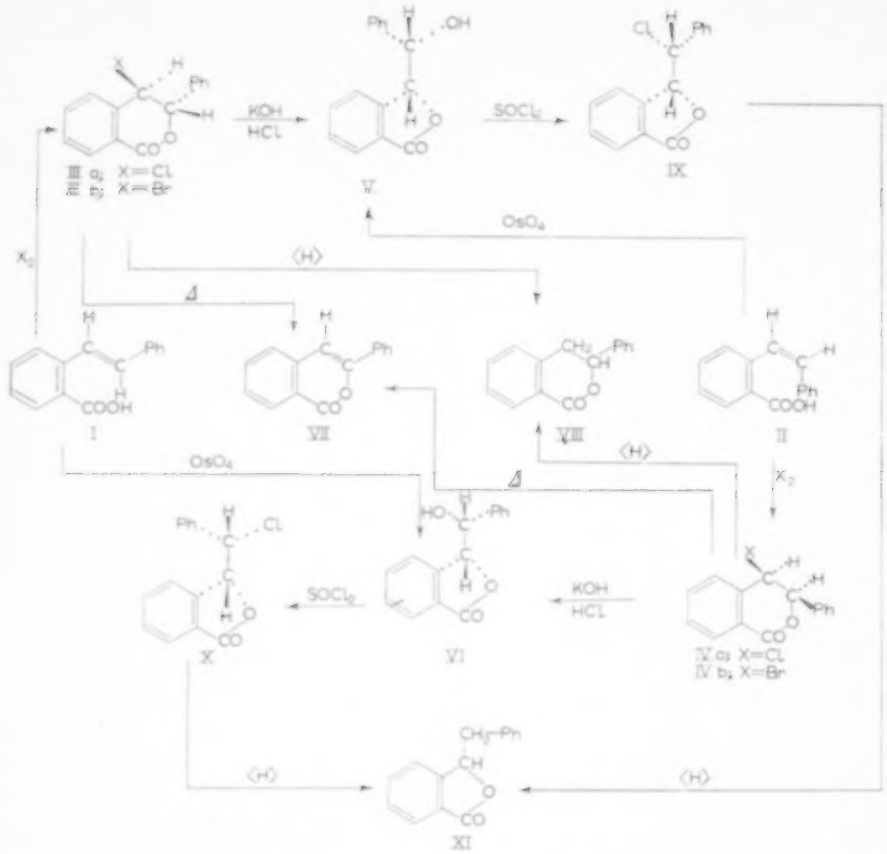
Abstract—The stereochemistry of the reaction of *cis*- and *trans*-stilbene-2-carboxylic acids with chlorine and bromine, yielding the two diastereoisomeric 3-phenyl-4-halo-3:4-dihydro*iso*coumarins (III) and (IV) has been investigated. The reactions are entirely stereospecific and involve intramolecular attack by the carboxyl group on an intermediate carbonium or halonium ion. The lactones (III) and (IV) yield the two 3-(α-hydroxybenzyl) phthalides (V) and (VI), with retention of configuration. Thionyl chloride transforms (V) and (VI) into the 3-(α-chlorobenzyl) phthalides (IX) and (X), with inversion. Steric effects are mainly responsible for the alternative formation of halolactones or normal dihalogenated derivatives in the reactions between unsaturated acids and halogens.

PREVIOUS work has shown[1] that halogenated phthalides are obtained in the reaction of chlorine or bromine with a series of derivatives of *o*-(α-phenylvinyl) benzoic acid. In order to understand the stereochemistry and mechanism of halolactonisations, the reaction has been applied to *trans*-stilbene-2-carboxylic acid (I) and its *cis*-isomer[2] (II).

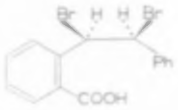
X = H, Cl, Br
R = CH_3, C_2H_5, C_6H_5

The acids (I) and (II) are almost quantitatively transformed by chlorine into chlorolactones of the formula $C_{15}H_{11}O_2Cl$, the *trans*-acid giving exclusively one, m.p. 110°, the *cis*-acid another, m.p. 147°. These lactones are not phthalides, as in the previously described cases,[1] but δ-lactone structures (IIIa) and (IVa), because, on pyrolysis, both give 3-phenyl*iso*coumarin (VII), and, on catalytic hydrogenation, 3-phenyl-3:4-dihydro*iso*coumarin (VIII). The reaction of (I) with bromine is described by Leupold,[3] who isolated a dibromoacid. Repetition of the bromination of (I), and (II), showed that Leupold's dibromoacid (XII) is formed from both (I) and (II),

[1] G. Berti, *Gazz. Chim. Ital.* **81**, 305 (1951).
[2] G. Berti, *Gazz. Chim. Ital.* **86**, 883 (1956).
[3] E. Leupold, *Ber. Dtsch. Chem. Ges.* **34**, 2829 (1901).



in variable amounts, depending on the solvent, (in the chlorination reactions the corresponding dichloroacid was not isolated). The *erythro*-configuration (XII) is assigned to the dibromoacid, as it is transformed by sodium iodide into *trans*-stilbene-2-carboxylic acid (I). Beside (XII), substantial amounts of bromolactones



XII

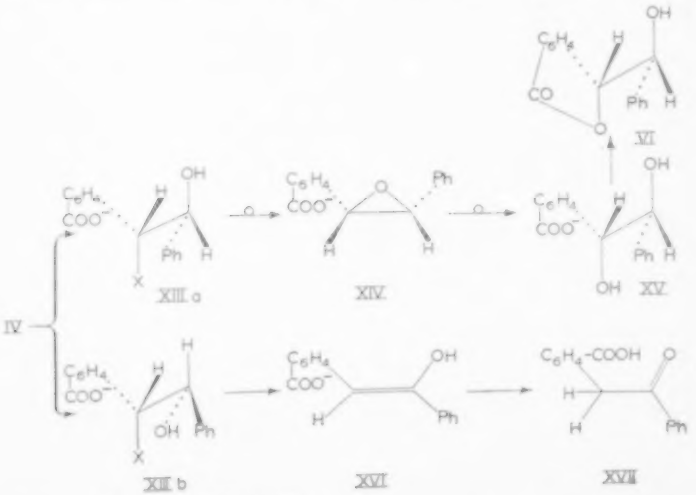
(III b) and (IV b) were obtained from these brominations: one, m.p. 92°, from the *trans*-acid and one, m.p. 138°, from the *cis*-acid, identical with the one prepared by Leupold from (XII).

These halolactonisation reactions are noteworthy, as the products are formed in a completely stereospecific way, because it is known that electrophilic additions to stilbene derivatives are not at all specific from the stereochemical point of view.[4]

[4] G. W. Wheland, *Advanced Organic Chemistry* p. 292. Wiley, New York (1949).

Treatment of the halolactones (III) and (IV) with ethanolic potassium hydroxide, followed by acidification, gives the hydroxyphthalides (V) and (VI). The lower-melting chloro- and bromolactones, obtained from the *trans*-acid (I), are quantitatively transformed into a hydroxyphthalide, m.p. 149°, the higher melting ones give the other phthalide, m.p. 103°, and substantial amounts of *o*-phenacylbenzoic acid (XVII). Both (V) and (VI) on pyrolysis give phthalide and benzaldehyde, in fairly good yield. Treatment with thionyl chloride transforms (V) and (VI) into the diastereo-isomeric chlorophthalides (IX) and (X), which, on catalytic reduction, yielded 3-benzylphtalide (XI).

The higher-melting bromolactone, obtained from *cis*-stilbene-2-carboxylic acid (II), is transformed almost quantitatively into 3-phenyl*iso*coumarin (VII), when refluxed with an alcoholic solution of potassium acetate, whilst its diastereoisomer is recovered unchanged from the same treatment, indicating a *trans*-disposition of halogen and β-hydrogen in the former lactone. Consequently, the higher melting halolactones obtained from (II) should have configuration (IV). This is further confirmed by the fact, that only the halolactones derived from (II) give with potassium hydroxide the salt of *o*-phenacylbenzoic acid (XVII). In order to explain this difference it is necessary to examine the probable mechanisms of the two alternative reactions, the one leading to the salt of α,α'-dihydroxydibenzyl-2-carboxylic acid (XV) and the other yielding the salt of (XVII). The first step in the reaction of strong bases with (III) and (IX) is the opening of the lactone rings, with formation of the corresponding hydroxyhaloacids. The lactones with configuration (IV) are therefore transformed into (XIII), which on further action of the base yields (XV), probably through an intermediate epoxide (XIV), in accordance with the accepted mechanism for the conversion of halohydrins into glycols.[5] When the solution of (XV) is acidified, the more stable γ-lactone (VI) is formed. The ion (XIII) can also lose hydrogen chloride to form the enol (XVI), instead of the epoxide (XIV); the enol, when treated with acid, gives (XVII). It is evident that, starting from lactones of type (IX), the conformation (XIII a), leading to (XIV), is sterically hindered, and the two aromatic



[5] P. Bartlett, *J. Amer. Chem. Soc.* **57**, 224 (1935).

groups are *cis* to each other in the transition state, while the conformation (XIII b) leads to (XVII), through a transition state free of such hindrance. The opposite situation will apply to the lactones of type (III). The fact that the latter do not yield even traces of the acid (XVII) is therefore in agreement with the assigned configurations. An alternative mechanism for the formation of (XVII) from (IV), involving first the elimination of hydrogen chloride or bromide from the halolactones, followed by the opening of the ring of the 3-phenyl*iso*coumarin thus formed, to give (XVI), would lead to the same conclusions.

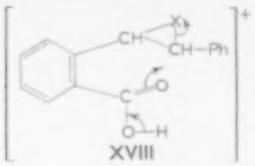
The mechanism proposed for the conversion of the halolactones (III) and (IV) to the hydroxyphthalides (V) and (VI), involving two inversions, should lead to products having the same configurations as the starting materials. This was proved by treating the acids (I) and (II), and their methyl esters, with osmium tetroxide.[6] It was not possible to isolate the dihydroxylated acids, but the products had the hydroxylactonic structures (V) and (VI); only the higher-melting hydroxyphthalide (V) was obtained from the *cis*-acid, and the lower-melting one from the *trans*-acid. The *cis*-dihydroxylation product from the *cis*-acid has the *erythro*-configuration, corresponding, after lactonisation, to (V), the one from the *trans*-acid the *threo*-configuration, leading to (VI), in agreement with the hypothesis that the *erythro*-compound has the higher melting point.

The configurations of the two chlorophthalides (IX) and (X), obtained from (V) and (VI) with thionyl chloride, can be assumed with fair certainty from a comparison of the melting points, showing that the replacement of the hydroxyl group by chlorine takes place with inversion: the chlorophthalide, m.p. 107°, is obtained from (V), and should have the *threo*-configuration (IX), while the other chloro-derivative, is formed from (VI), and should therefore be the *erythro*-form (X).

The possibility that the halolactones are formed through an elimination of HCl or HB_2 from dihalogenated acids of type (XII) can be ruled out. Such a mechanism should give halolactones with opposite configurations of those found, assuming that one of the halogen atoms is displaced by the carboxyl group with inversion. This happens in the case of the transformation (XII) → (IV b), and Weinstock[7] showed that the pyrolytic transformation of γ-bromoesters into lactones takes place with inversion. The same isomer of (XII) being obtained in the bromination of (I) and (II), clearly shows that (XII) cannot be an intermediate in a stereospecific halolactonisation; furthermore, (XII) is stable under the conditions used for the reactions and is lactonised only on prolonged heating of its acetic acid solution.

An acceptable mechanism must involve an attack by the carboxyl group on the intermediate ion formed by interaction between the halogen and the double bond. This ionic intermediate could be either a halonium ion,[8] (XVIII), or a π-complex[9] or an open carbonium ion, provided that the attack by the carboxyl group takes place more rapidly than the rotation around the α,β-bond, to account for the observed stereospecificity. A restriction of such rotation could be explained by an electrostatic interaction between the positive centre and the halogen atom, according to de la Mare and Pritchard.[10] A mechanism of this type had been assumed in our previous

[6] N. A. Milas and S. Sussmann, *J. Amer. Chem. Soc.* **59**, 2345 (1937).
[7] J. Weinstock, *J. Amer. Chem. Soc.* **78**, 4967 (1956).
[8] I. Roberts and G. E. Kimball, *J. Amer. Chem. Soc.* **59**, 947 (1937).
[9] M. J. S. Dewar, *Disc. Faraday Soc.* **2**, 75 (1947).
[10] P. B. D. de la Mare and J. G. Pritchard, *J. Chem. Soc.* 3910, 3990 (1954).



XVIII

paper,[1] and later by Craig[11] and by van Tamelen and Shamma[12] for different types of halolactonisations. In such a mechanism the attack by the carboxyl group should take place on the side opposite to the halogen atom, and this is now substantiated by the observed steric course of the reactions. The formation of the dibromo-acid (XII) and not of a dichloroacid as a side-product is explained by the more nucleophilic character of the bromine anion, compared to the chlorine anion, allowing the former to compete successfully with the carboxyl group in the attack on the intermediate cation.

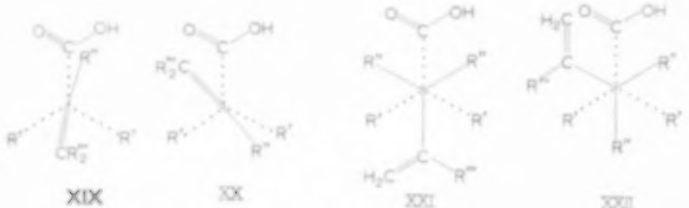
It appears that halolactonisation is the rule, when derivatives of *o*-vinylbenzoic acid are treated with halogens. Data in the literature show, that the formation of normal dihalogenated products is the usual reaction with most other types of unsaturated acids, unless the halogenation is carried out under special conditions. The best known and most widely studied example is the formation of iodolactones in the treatment of alkaline solutions of unsaturated acids with iodine,[13] recently reviewed by van Tamelen and Shamma.[12] In this case the more open nucleophilic character of the carboxyl anion facilitates the reaction so, that it can be applied to most β,γ- and γ,δ-olefinic acids. Less frequently bromo- or chlorolactones are formed directly from free acids or from esters. In addition to the reactions discussed, the following cases of monocarboxylic acids, giving halolactones directly, are reported in the literature:[14–17] Dicarboxylic acids such as diallylamalonic,[14] benzyl-allylmalonic and its esters[18] and several derivatives of itaconic[19,20,21,22] and aticonic acids[23,24] yield halolactones. It is probable that the halolactones prepared by Gaudry and Godin[25] from esters of allymalonic acid are formed from the dihalogenated esters during the distillation to which the reaction products are subjected, as it is known that γ- and δ-haloesters are easily transformed into lactones[26] and that allylmalonic acid gives a stable dibromoderivative.[14]

A common feature of most of the acids giving halolactones is the presence of two substituents, or a large one, in the α-positions. This applies to both β,γ- and

[11] P. N. Craig, *J. Amer. Chem. Soc.* **74**, 129 (1952).
[12] E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.* **76**, 2315 (1954).
[13] J. Bougault, *Ann. Chim. Phys.* **14**, 145 (1908); **15**, 296 (1908).
[14] R. Fittig and E. Hjelt, *Ann.* **216**, 52 (1882).
[15] W. H. Perkin and A. Smith, *J. Chem. Soc.* **85**, 155 (1904).
[16] P. N. Craig and I. H. Witt, *J. Amer. Chem. Soc.* **72**, 4925 (1950).
[17] A. Winterstein and W. Hämmerle, *Z. Physiol. Chem.* **199**, 56 (1931).
[18] R. T. Arnolds, M. de Moura Campos and K. L. Lindsay, *J. Amer. Chem. Soc.* **75**, 1044 (1953).
[19] R. Fittig, *Ann.* **226**, 366 (1884).
[20] H. Stobbe, *Ann.* **308**, 77 (1899).
[21] R. Fittig, *Ann.* **331**, 142 (1904).
[22] H. Stobbe, *Ann.* **321**, 119 (1902).
[23] R. Fittig, *Ann.* **304**, 222, 311 (1898).
[24] H. Stobbe, *Ann.* **308**, 77, 82 (1899).
[25] R. Gaudry and C. Godin, *J. Amer. Chem. Soc.* **76**, 139 (1954).
[26] V. Grignard, *Traitè de Chimie Organique* Vol. 11, p. 82. Masson, Paris (1945).

γ,δ-unsaturated acids; thus, while 3-pentenoic[27] and 4-pentenoic acids[28] give normal dibromoderivatives with bromine, 2:2-dimethyl-3-pentenoic and 2:2-diphenyl-4-pentenoic acids, yield bromolactones. These are examples of the so-called "*gem* group effect", which facilitates cyclisations. There can be little doubt that this difference in behaviour is entirely due to steric effects, as the size of the groups seems to be more important than their type. Only if in the intermediate cation the carboxyl group and the positive centre are near enough to enter rapidly into the transition state leading to the lactone ring, formation of the halolactone can take place; otherwise, the cation is attacked by a halogen anion and a dihalogenated compound is formed.

It can be assumed that the most stable conformation for β,γ-unsaturated acids, having no substituents α to the carboxyl group (R′ = H) and with R″ small, is (XIX);



XIX XX XXI XXII

as, however, the R′ groups become radicals of increasing steric requirements, configuration (XX) should be favoured, unless R″ also increases. Only in the latter conformation the carboxyl group and double bond are near enough to allow cyclisation of the intermediate ion to occur rapidly enough to avoid reaction with the halogen anion. A similar explanation also holds for γ,δ-unsaturated acids, as shown by the conformations (XXI) and (XXII). If one of the R′ groups is a carboxyl group or a second unsaturated group, cyclisation is again facilitated, since in any of the possible conformations a carboxyl group and a double bond are near enough to produce cyclisation; this explains the higher tendency to halolactonisation of derivatives of malonic and of diallylacetic acid. A particular case in favour of the above hypothesis is that of the derivatives of aticonic acid (XXIII), in which lactonisation can take place through two different carboxyl groups; in all cases described in the literature[23,24] only the lactones of type (XXIV) are formed, that is, those involving the carboxyl group attached to the most heavily substituted carbon atom.

The analysis made does not take into account the sizes of the groups R″ and R‴, but the line of reasoning can be extended to foresee their effects. Too few cases are known to allow of a more general theory. The effect of *gem*-groups, favouring

XXIII XXIV

other cyclisation reactions, is explained in a somewhat similar way by Hammond.[29]

Derivatives of *o*-vinylbenzoic acid, (I) and (II) have a particular tendency to give

[27] R. Fittig and J. E. Mackenzie, *Ann.* **283**, 97 (1894).
[28] R. Fittig and A. Messerschmidt, *Ann.* **208**, 92 (1881).
[29] M. S. Newman (Editor), *Steric Effects in Organic Chemistry* p. 468. Wiley, New York (1956).

halolactones, as the carboxyl and vinyl groups are forced in the *cis*-position by the benzene ring to which they are attached. This should lead to a very rapid interaction between the carboxyl group and the positive centre and may account for the observed stereospecificity. The great tendency towards formation of the lactone ring is confirmed by the fact that the methyl esters of (I) and (II) give only the halolactones, when treated with halogens. Until it is established that all types of halolactonisations proceed by the same mechanism, no general conclusions can be drawn. No kinetic data is available, nor are there any other stereochemical studies.*

EXPERIMENTAL

Melting points were determined on the Kofler block.

trans-*Stilbene-2-carboxylic acid* (I) was prepared from 3-benzylphthalide with potassium hydroxide;[30] *cis*-stilbene-2-carboxylic acid (II) by isomerisation in sunlight of the *trans*-acid.[2]

Methyl trans-*stilbene-2-carboxylate*. Acid (I, 3·5 g) and thionyl chloride (10 ml) were heated at 60° for 2 hr, the excess chloride was distilled off under reduced pressure, the residue treated with anhydrous methanol (15 ml) and dimethyl-aniline (3 ml) and refluxed for 1 hr. The methanol was distilled off, the residue poured into water, extracted with ether, washed with hydrochloric acid, water and sodium carbonate solution, dried on magnesium sulphate and distilled; an oil, b.p. 168–170°/0,5 mm, was obtained (Found: C, 80·15; H, 5·64. $C_{16}H_{14}O_2$ requires C 80·64; H, 5·92%). *Methyl* cis-*stilbene-2-carboxylate* was prepared in a similar manner.[31]

trans-3-*Phenyl*-4-*chlorodihydro*isocoumarin (III a). Dry chlorine was passed through a solution of *trans*-stilbene-2-carboxylic acid (2·0 g) in chloroform (30 ml) for 20 min; much hydrogen chloride was evolved. After washing with sodium carbonate solution (the alkaline layer did not precipitate on acidification) and drying on magnesium sulphate, the solvent was evaporated. Crystallisation of the residue from benzene-ligroin yielded needles (1·85 g), m.p. 108–110° (Found: C, 69·70; H, 4·46; Cl, 13·46. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29; Cl, 13·70%). Also when the reaction was repeated under different conditions (low temperature, avoiding excess of chlorine, using acetic acid or carbon tetrachloride as solvents, etc.) the only product was (III a), and in no case was it possible to isolate a dichloro-acid. Only the chlorolactones (III a) was also obtained in the chlorination of the methyl ester of the acid (I) in chloroform solution.

cis-3-*Phenyl*-4-*chlorodihydro*isocoumarin (IV a). The chlorination of *cis*-stilbene-2-carboxylic acid (3 g), as described for the *trans*-acid, yielded a neutral product (3·1 g) which crystallised from ethanol in stout needles, m.p. 146–147° (Found: C, 69·44; H, 4·55. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29%). The same product was obtained from the chlorination of the methyl ester of the acid (II).

trans-3-*Phenyl*-4-*bromodihydro*isocoumarin (III b). A solution of the acid (I, 1·0 g) in acetic acid (20 ml), cooled with ice, was treated with bromine (0·8 g) in acetic

* Only one other case has been found in the literature, in which the halolactonisation reaction has been applied to a couple of *cis-trans* isomers: of the two forms of γ-methyl-γ-phenylitaconic acid each gives a different diastereoisomeric lactone.[24] This is a further proof of the stereospecificity of the reaction, even if the configurations given by Stobbe to the two lactones probably are wrong, as he supposes that they were formed as secondary products from the cyclisation of the dibromoacids.

[30] S. Gabriel and T. Posner, *Ber. Dtsch. Chem. Ges.* **27**, 2506 (1894).
[31] D. F. DeTar and L. A. Carpino, *J. Amer. Chem. Soc.* **78**, 475 (1956).

acid (5 ml), rapidly and with stirring. After 15 min the mixture was filtered, allowing the acetic acid to melt on the filter. The dibromoacid (XII, 0·45 g), m.p. 180°, was thus obtained. The filtrate, on dilution with water, separated an oil, which solidified on standing. Recrystallisation from light petroleum, containing a little benzene, yielded needles, m.p. 90–92° (0·7 g). (Found: Br, 26·31. $C_{15}H_{11}O_2Br$ requires Br, 26·36%). When the bromination was carried out in carbon tetrachloride at −10°, the acid (I, 0·5 g) yielded (XII, 0·7 g) and (III b, 0·1 g). When chloroform was used as the solvent, (XII, 0·15 g) and (IV b, 0·4 g) were obtained from (I, 0·4 g).

cis-3-*Phenyl*-4-*bromodihydroisocoumarin* (IV b). A solution of *cis*-stilbene-2-carboxylic acid (II, 2 g) in chloroform (20 ml) was treated with bromine (1·6 g) in chloroform (5 ml). A small amount of the dibromoacid (XII) separated out and was filtered off. The solution, after elimination of the solvent, gave a residue, which, taken up in light petroleum, yielded 1·85 g of a product, m.p. 136–138°, which had been previously described by Leupold,[3] who obtained it on refluxing an acetic solution of (XII). Using carbon tetrachloride as the solvent for the bromination, (II, 0·5 g) yielded (XII, 0·45 g) and only traces of the lactone (IV b). Refluxing the dibromoacid (XII) for one hr in acetone or chloroform, left it unchanged.

Proofs of structure of the lactones (III) *and* (IV). All four halolactones (III a and b, IV a and b) were subjected to pyrolysis and yielded 3-phenyl*iso*coumarin (VII). The method followed for (III a) was the following: the compound was heated in an open vessel at 220–250° until foaming ceased and the residue was recrystallised from ethanol, and then from light petroleum. A product, m.p. 89–90°, was thus obtained, which did not depress the melting point of an authentic sample of (VII). The same result was obtained with the other lactones, the bromo lactones requiring a lower temperature (180–200°) for pyrolysis. The transformation of (IV B) into (VII) has been described by Leupold.[3]

The bromolactone (IV b) was transformed into 3-phenyl*iso*coumarin as follows: a solution of (IV b 0·2 g) and potassium acetate (0·2 g) in ethanol (5 ml) was refluxed during 30 min. Potassium bromide separated out. On dilution with water a product, containing only traces of bromine was obtained, which after one crystallisation from light petroleum-benzene, gave (VII), m.p. 89–90°. On the other hand the bromolactone (III b) was recovered unchanged from such a treatment.

The chlorolactones (III a) and (IV a) were also transformed into 3-phenyl-3:4-dihydro*iso*coumarin (VIII) in the following way: a solution of (III A, 0·6 g) in ethanol (20 ml) was hydrogenated at atmospheric pressure, in the presence of 5% palladiated carbon (0·15 g). The hydrogenation was stopped when a 30% excess of the equimolar quantity of hydrogen had been absorbed. (It is not convenient to stop the hydrogenation after absorption of the equimolar quantity, as at this stage a substantial amount of the starting material, which is difficult to separate from (VIII), is still present). The catalyst was filtered off, the solvent eliminated on a steam-bath, the residue treated with sodium carbonate solution and filtered. The product was crystallised twice from aqueous ethanol, yielding 0·2 g of a product, m.p. and mixed m.p. with (VIII), 89–90°. The alkaline solution, an acidification and crystallisation of the precipitate from benzene-light petroleum, yielded 0·2 g of dibenzyl-*o*-carboxylic acid, m.p. 130–131°, formed by hydrogenolysis of the lactone ring of (VIII). The same results were obtained in the reduction of (IV a).

The dibromoacid (XII, 0·1 g), dissolved in acetone, was treated with a 15%

solution of sodium iodide in acetone and refluxed for 30 min. After dilution with water a product precipitated, which was crystallised from ethanol, yielding needles, m.p. 158–160°, of *trans*-stilbene-2-carboxylic acid (I).

erythro-3-(α-*Hydroxybenzyl*) *phthalide* (V). A solution of the lactone (III a, 3·0 g) in 10% alcoholic potassium hydroxide (30 ml) was refluxed for 30 min, then diluted with water and acidified with sulphuric acid. The precipitate, which was insoluble in cold sodium hydroxide, was crystallised from benzene-petroleum ether, yielding needles, m.p. 148–149° (2·6 g). (Found: C, 74·86; H, 5·30. $C_{15}H_{12}O_3$ requires C, 74·99; H, 5·04%). The same product was obtained from the lactone (III B) in a similar way.

Compound (V) was also obtained as follows: a solution of the methyl ester of the acid (II, 0·1 g) and pyridine (0·2 ml) in anhydrous ether (3 ml) was treated with a solution of osmium tetroxide (0·1 g) in ether (3 ml). A yellow colour appeared immediately, and after a few minutes a precipitate started to separate. After 48 hr at room temperature, the light brown precipitate was collected, washed with ether, dissolved in dichloromethane (5 ml) and treated with a solution of sodium hydroxide (0·2 g) and mannitol (0·5 g) in water (8 ml). After shaking until it was decolourised, the organic layer was dried with magnesium sulphate, evaporated to dryness and the residue crystallised from benzene-petroleum ether, yielding a product, m.p. 148–149°, identical with the one described above. A further quantity of the same compound was obtained on acidification of the aqueous layer and extraction with ether. The same result was also obtained with the Milas method.[6] To a solution of hydrogen peroxide in tertiary butanol, prepared in the usual way[32] from the alcohol (10 ml) and peroxide (3 ml, 30%), *cis*-stilbene-2-carboxylic acid (3·5 g) and osmium tetraoxide (10 mg) were added, the mixture was heated to 50° until solution was complete and left at room temperature during 48 hr. Water was added, the solution extracted with benzene, the benzene layer washed with sodium carbonate solution and evaporated. Addition of ligroin to the residue gave product (V, 2·2 g).

Threo-3-(α-*hydroxybenzyl*) *phthalide* (VI). A solution of the chlorolactone (IV a, 1·5 g) in alcoholic potassium hydroxide (10 ml, 10%) was refluxed 5 min, then diluted with water and acidified. The precipitate was collected and treated with sodium carbonate solution. The residue (0·7 g), after crystallisation from benzene-ligroin, had m.p. 102–103° (Found: C, 74·63; H, 5·48. $C_{15}H_{12}O_3$ requires C, 74·99; H, 5·04%). Acidification of the alkaline solution yielded needles (0·3 g), which, after crystallisation from benzene, had m.p. 160° with decomposition; they were identified as *o*-phenacylbenzoic acid (XVII) by the mixed m.p. with an authentic sample.[33] When the reaction was repeated with bromolactone (IV, b, 0·5 g) only (VI, 0·1 g) was obtained, together with (XVII, 0·23 g).

Compound (VI) was further obtained when a solution of *trans*-stilbene-2-carboxylic acid (0·05 g) in anhydrous ether (1·5 ml), containing pyridine (0·1 ml), was treated with a solution of osmium tetroxide (0·05 g) in ether (1·5 ml). An amorphous brown precipitate was formed at once, which, after 48 hr at room temperature, had become crystalline. The osmic ester was decomposed as described above. The aqueous layer, after acidification and extraction with ether, gave a product, melting at 102–103°, identical with the one described above. The same product was also

[32] A. I. Vogel, *Practical Organic Chemistry* p. 895. Longmans, London (1956).
[33] S. Gabriel, *Ber. Dtsch. Chem. Ges.* **18**, 2446 (1885).

obtained from (I), using hydrogen peroxide and trace amounts of osmium tetroxide.

Transformation of (V) *and* (VI) *into phthalide and benzaldehyde.* The lactone (V, 1 g) was heated rapidly in an alloy bath with a small distillation flask. When the bath temperature reached 280° decomposition became evident and a liquid, having all the characteristics of benzaldehyde (0·4 g, yielding a DNP, m.p. 237–238°) distilled. When the temperature reached 360°, another fraction distilled, which solidified on scratching, yielding a compound (0·3 g), melting, after recrystallisation from water, at 72° (phthalide). The isomeric hydroxylactone (VI) gave pthalide and benzaldehyde too, but decomposition started only at 300° and the yields were lower.

threo-3-(α-*Chlorobenzyl*) *phthalide* (IX). A solution of the lactone (V, 0·5 g) in thionyl chloride (2 ml) was refluxed for 30 min, then poured on ice. The precipitate was extracted with ether, dried on magnesium sulphate, and the ether was distilled off; the residue was taken up in benzene and fractionally precipitated with petroleum ether. After decantation from a first oily fraction, needles (0·2 g) were obtained, which, after a second crystallisation from the same solvent mixture, had m.p. 106–107° (a mixture with the chlorolactone (III a) had m.p. 85–90°) (Found: C, 69·83; H, 4·35; Cl, 14·0. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29; Cl, 13·7%).

erythro-3-(α-*Chlorobenzyl*) *phthalide* (X). It was obtained from the hydroxylactone (VI, 0·5 g), on refluxing with thionyl chloride (3 ml) for 10 min, evaporating under reduced pressure at room temperature and recrystallising the residue from a little methanol: 0·3 g, m.p. 147–148° (mixed m.p. with (IV a, 115–120°). (Found: C, 69·46; H, 4·60; Cl, 13·4. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29; Cl, 13·7%).

Both (IX) and (X) were reduced with palladium on carbon, as described above, yielding 3-benzylphthalide, m.p. 60–61°.

Tetrahedron, 1958, Vol. 4, pp. 403–417. Pergamon Press Ltd., London

ELECTRONIC SPECTRA OF ORGANIC MOLECULES AND THEIR INTERPRETATION—IV*

EFFECT OF TERMINAL ATOMS WITH LONE ELECTRON PAIRS ON THE K-BANDS OF CONJUGATED SYSTEMS

A. BURAWOY, J. P. CRITCHLEY and A. R. THOMPSON
Manchester College of Science and Technology

(*Received* 1 *July* 1958)

Abstract—The effect of the hydroxyl, methoxyl, mercapto, methylmercapto, and amino groups as well as of the charged O^- and S^- atoms (X) at the ends of the conjugated systems (1) and (2) on the position of the corresponding K-bands is discussed.

$$\xrightarrow{p\text{-}X\text{—}C_6H_4\text{—}B} \quad (B = H, NO_2, \overset{+}{N}H_3) \tag{1}$$

$$\xrightarrow{p\text{-}A\text{—}C_6H_4\text{—}X} \quad (A = SMe, NH_2, SH, O^-, \text{or } S^-) \tag{2}$$

The conclusions of earlier investigations are confirmed. The "effective" electron migration in one direction along the absorbing conjugated system (indicated by the long arrow) determines almost exclusively the stability of the observed excited state. The displacement of a K-band to longer wavelengths on introduction of a terminal group (X) can be due either to an electron shift in the substituted system coinciding with the direction of the effective electron migration of the transition or to an increased electron polarisability of the terminal group itself.

A consistent qualitative, but very detailed, theoretical interpretation of these observations is possible by a consideration of the electronic perturbations in the excited state due to Heisenberg resonance, if the molecules are accepted as being built up of localised bonds and involving inductive (inductomeric) electron shifts only.

1. INTRODUCTION

INVESTIGATIONS of the effect of terminal methyl groups,[1] substituted methyl groups,[2] and of the halogen atoms[3] of absorbing (conjugated) systems such as (I) on the position of the corresponding absorption bands of high intensity (K-bands) have provided evidence that the "effective" electron migration in one direction along the absorbing system determines the transition energy (stability of the excited state). The contribution of the accompanying "complementary" electron migration in the opposite direction is only small and can, generally, be neglected in qualitative comparative discussions.

$$\xrightarrow{A\text{—}[CH{=}CH]_n\text{—}B} \quad (A \text{ or } B:\ CH_3,\ CH_2X,\ F,\ Cl,\ Br,\ I) \qquad \text{I}$$

It has also been shown that the displacement of a K-band to longer wavelengths on structural modification of the terminal groups (I, A–C or C–B) can be due to two factors: (a) Electron shifts (in the ground state) of the substituted system which will

* *Tetrahedron* **2**, 122 (1958) is considered as Part III of this series.
[1] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2085 (1955).
[2] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2557 (1955).
[3] A. Burawoy and A. R. Thompson, *J. Chem. Soc.* 4314 (1956).

increase its electronic polarisability (and facilitate the electron migration) in this direction. (b) An increase of the electronic polarisability of the terminal group itself.

The reported observations cannot be consistently accounted for by the widely-accepted theoretical interpretations based on molecular structures involving non-localised bonds (resonance among several idealised valence-bond structures, many-centred molecular orbitals), on mesomeric electron displacements, and on the simplifying assumption that only the π electrons are important or need to be considered for the electronic transition. However, a qualitative, but very detailed, understanding of these and other observations related to the electronic spectra of organic molecules becomes possible by consideration of the mathematically well-established effects resulting from the electronic perturbations in an excited state attributable to Heisenberg resonance, if organic molecules are accepted as being built up of localised bonds and as involving inductive electron shifts only.[4]

According to this view, the normal excited state of a molecule of type (I) corresponding to a K-band can be represented as a "hybrid" of unperturbed states each involving one excited electron. It is possible, for convenience, to indicate this by one formula only (II), in which the excited electron of each unperturbed state is shown by one arrow, simultaneously indicating the symmetry of the excited orbital as well as the direction of the charge migration on one side of the nodal plane formed. Ignoring the branching C—H bonds, the contribution of the $(2 + 6n)$ unperturbed states to the "hybrid" will be proportional to their stability but, in the first instance, only states involving neighbouring excited electrons will interact.

II III

The excited orbital of each unperturbed state is divided by a nodal plane into two parts corresponding to wave-functions of opposite sign. In an unsymmetrical bond, it will extend to a different degree on both sides of the nodal plane formed. In valence-bond terminology, this would be equivalent to the statement that in the excited state of a molecule $\overset{\delta+}{A}—\overset{\delta-}{B}$ described as a hybrid $\overset{+\ -}{AB} \leftrightarrow \overset{-\ +}{AB}$, the stability (and contribution to the hybrid) of $\overset{+\ -}{AB}$ is different from and greater than that of $\overset{-\ +}{AB}$.

The *degree of interaction* will increase, the lower and energetically nearer each pair of interacting (unperturbed) energy levels are, but, in the first instance, only their part-orbitals in phase with the effective electron migration of the transition, the direction of which is indicated by the arrows, will be important. Thus, if A and B in (II) are identical, e.g. halogen or hydrogen atoms, the unperturbed energy levels involving the excited electrons of the unsymmetrical bonds A—*C* and *C*—B will be equal. However, the degree of interaction (determining the degree of stabilisation of the normal excited state) will be different, since it depends on the different extension (stability) of the excited orbital on both sides of the dividing nodal plane. (This corresponds to the different electron polarisability in the two directions of these bonds.)

The factors determining the *stability* of the normal excited state are (i) the most

[4] A. Burawoy, *Tetrahedron* **2**, 122 (1958).

stable (the "basic") unperturbed excited state and (ii) the degree of its interaction with the unperturbed states involving excited neighbouring electrons. Again, the stability of the latter will be modified by interaction with other neighbouring states, the effect of which is transmitted along the whole absorbing system.

The empirical conclusion that the electron migration in one direction of the absorbing system determines the stability of the normal excited state indicates that the additional stabilisation arising from the interactions of the part-orbitals corresponding to the complementary electron migration of the system (cf. III) is only negligible. It should be expected to be greatest if the difference between the two energy levels corresponding to the artificially separated combined part-orbitals of the absorbing system (e.g. II and III) is very small. In such a case, it sometimes becomes apparent and has to be taken into account even in qualitative comparative discussions, if only small differences ($<$50 Å) are under consideration. A more detailed discussion of this matter and experimental evidence for the reality of this effect will be given elsewhere.

This interpretation also accounts for the fact that any electron shift in the ground state of an absorbing system or individual bond (as, e.g., caused by a change of the terminal group or by a solvent) increases the electronic polarisability in the direction of the shift (and reduces it in the opposite direction) and, thus, dependent upon the direction of the effective electron migration of the transition, stabilises (or otherwise) the normal excited state. This indicates that in each bond the increased stability of the part-orbitals in phase with the effective electron migration of the transition, which results from the reduction of the ionisation potential of the "donating" atom and/or the increase in the electron affinity of the "receiving" atom, is the determining factor (for details, cf. reference 4).

In the present paper, the discussion is extended to the effect of terminal groups involving atoms with unshared electrons (other than the already discussed halogen atoms[3]) (I, A or B = OH, OMe, SH, SMe, NH_2, O^-, S^-) on the position of the corresponding K-bands. However, for purposes of comparison, reference to the effect of the fluorine atom will also be made.

2. EFFECT OF ELECTRON-DONATING TERMINAL GROUPS OF THE EFFECTIVE ELECTRON MIGRATION

(a) *Mono-substituted benzene derivatives*

Data for the maxima and intensities of the K-bands of benzene, fluorobenzene, phenol, anisole, thiophenol, thioanisole, and aniline in hexane and ethanol and of the phenoxide and thiophenoxide ions in ethanol and water, as well as the displacements (D) of the benzene K-band (2020/2035 Å in various solvents) to longer wavelengths on substitution, are shown in Table 1.

The electron-repelling power of the substituents (X) in these compounds (IV) increases approximately in the order $F \ll OH < OMe \sim SH < SMe < H < NH_2 \ll O^-, S^-$. In phenol, anisole, thiophenol, and thioanisole, the hydroxyl, methoxyl, mercapto, and methylmercapto groups respectively should be slightly electron-attracting compared with the hydrogen atom, since the groups, on introduction into the *m*-position, are known to increase the acidity of phenol and even of benzoic acid.[5]

[5] H. C. Brown, D. H. McDaniel and O. Häfliger, *Determination of Organic Structures by Physical Methods* p. 588. Academic Press, New York (1955).

$$\xleftarrow{C_6H_5—X}$$

IV

The effective electron migration of the K-band transition is, undoubtedly, in all these examples directed towards the benzene nucleus (indicated by the arrow in IV), since this has already been shown to be true for fluorobenzene.[3] Thus, the electron-shift in the ground state of the substituted phenyl group should make a small decreasing negative contribution in the order F > OH > OMe ~ SH > SMe > H and an increasing positive contribution in the order H < NH_2 < O^- ~ S^- to the observed bathochromic displacement of the benzene K-band, although this effect should be insignificant in the case of the hydroxyl, methoxyl, mercapto, and methylmercapto groups.

It has already been shown in fluorobenzene that the bathochromic effect due to the greater polarisability of the C—F electrons towards the carbon atom as compared with that of the C—H electrons masks completely the displacement (in the case of fluorobenzene to shorter wavelengths) to be expected from the "polarity" factor mentioned. This should be true, to an even greater degree, for all other investigated substituents, since they contain much more strongly polarisable electronic systems.

The observed displacements of the benzene K-band to longer wavelengths indicate that the electronic polarisability towards the phenyl group increases in the order C—H < C—F (D, 48 Å in hexane; 38 Å in ethanol) < C—OH (98 Å; 160 Å) < C—OMe (178 Å; 165 Å) < C—NH_2 (320 Å; 314 Å) < C—O^- (—; 344 Å) < C—SH (346 Å; 345 Å) < C—SMe (511 Å; 510 Å < C—S^- (—; 650 Å).

Qualitatively, this order coincides in the case of C—F < C—OH < C—NH_2 and of C—OH < C—SH with the position of the atoms in the periodic table, i.e. the increasing electron repelling (decreasing electron attracting) character of the substituents. However, the electronic polarisability of the C—F, C—OH and C—OMe groups and of the C—SH and C—SMe groups is appreciably greater than that of the more strongly electron repelling C—H group and C—NH_2 and C—O^- groups respectively.

The observation that the K-band of thiophenol appears at only slightly longer wavelengths (2375 Å in ethanol) than the K-band of aniline (2344 Å) and that its position is similar to that of the phenoxide ion (2374 Å) is accounted for by a moderate, but greater contribution to the band displacements from the electron shift in the phenyl group (on substitution by the more strongly electron repelling NH_2 and O^- substituents) in the latter molecules (cf. also below).

Hydrogen bond formation. The K-bands of the phenoxide and the thiophenoxide ions are displaced to shorter wavelengths on replacing ethanol by water as solvent (29 and 60 Å respectively). All *p*-halogeno-phenoxide ions[3] and, as will be shown below, the *p*-methoxy-, *p*-amino-, and *p*-methylmercapto derivatives behave similarly (for data, cf. Table 3). This effect is due to the formation of stronger, and possibly multiple, hydrogen bonds of the charged atoms with water and the resulting reduction of both their electron repelling character and the polarisability of their unshared electrons. This change corresponds to the much greater one observed in the extreme case of proton addition, i.e. on formation of a hydroxyl or thiol group respectively. A systematic investigation of this matter will be reported elsewhere.

On the other hand, the appreciable displacement of the K-band of phenol to

longer wavelengths on replacing hexane by ethanol as solvent (72 Å) is, as already shown for many phenol derivatives,[6] due to hydrogen bond formation between the phenolic hydrogen atom and the oxygen atom of ethanol. This is responsible for an increase of the electron repelling character of the hydroxyl group as well as of the polarisability of the OH . . . OHEt electronic system. Again, this effect is qualitatively similar to the much greater one in the extreme case of complete ionisation, i.e. formation of the phenoxide ion.

No significant band displacement is observed for thiophenol indicating that the thiol group forms only a very weak, or no hydrogen bond with ethanol.

(b) p-*Nitrobenzene derivatives*

Data for the maxima of the K-bands of the *p*-nitrobenzene derivatives (V), the displacements of the maxima on introduction of the substituents (X), and the *differences* of the displacements observed in the benzene series and the *p*-nitrobenzene series (D*) are shown in the second column of Table 1. The effective electron migration corresponding to the K-band transition is always directed, as in the benzene derivatives, towards the phenyl group: This is indicated in (V) by a long arrow.

$$\xleftarrow{p\text{-}O_2N\text{—}C_6H_4\text{—}X}$$

V

Except for *p*-nitrofluorobenzene, the displacements of the K-bands to longer wavelengths on introduction of the investigated substituents (V, X = OH, OMe, SH, SMe, NH_2, O^-, S^-) into nitrobenzene are considerably greater than those observed in the benzene series, the differences (D*) being enhanced on replacing hexane by ethanol.

This is accounted for by two (artificially separated) effects. (1) The increased effective nuclear charge (electron deficiency) at the carbon atoms on introduction of the nitro-group, which is greater in ethanol than in hexane, is responsible for electron shifts in the terminal groups C—X (accompanied by changes of the interatomic distances and bond energies) and, thus, for an increase of their electron polarisability towards the carbon atom. As already shown,[3,7] these shifts involve an inductive mechanism and not a delocalisation of the orbitals of the unshared electrons (mesomeric effect). (2) The increased electron repelling character of the substituents (in turn) causes greater electron shifts in the substituted phenyl group. This, together with the even more important *additional* electron shifts within the C—NO_2 group, will result in a much greater increase of the electronic polarisability of the substituted nitrophenyl system as compared with that of the phenyl group in the corresponding benzene derivatives.

In contrast to all other substituents, which can be assumed to be electron repelling in the nitrobenzene series, the bathochromic effect due to the electron shift towards the carbon atom within the C—F bond on introduction of the nitro group is balanced by a hypsochromic effect due to the electron shift in the opposite direction within

[6] R. A. Morton and L. A. Stubbs, *J. Chem. Soc.* 1347 (1940); A. Burawoy and J. T. Chamberlain, *J. Chem Soc.* 2310, 3734 (1952); A. Burawoy, *Proceedings of the International Symposium on Hydrogen Bonding*. In press.

[7] A. Burawoy, *Trans. Faraday Soc.* **40,** 537 (1944); *Disc. Faraday Soc.* **10,** 104 (1951); *Chem. & Ind.* **63,** 434 (1944); *Contribution to the Study of Molecular Structure* p. 73. Desoer, Liège (1947–1948); A. Burawoy and E. Spinner, *J. Chem. Soc.* 3752 (1954).

TABLE 1. MAXIMA OF K-BANDS IN Å

X	Solvent		C_6H_5-X	$p\text{-}O_2N-C_6H_4-X$	$p\text{-}H_3\overset{+}{N}-C_6H_4-X$
H	EtOH	λ	~2030[a]	2595[b]	~2025[a]
		ε	—	9500	—
	C_6H_{14}	λ	2020[a]	2513[b]	—
		ε	6600	9000	
	H_2O	λ	2035[b]	2685[b]	2030[a]
		ε	7400	7800	7500
F[c]	EtOH	λ	2068	2622	2078
		ε	3000	9000	3400
		D	+38	+27	+53
		D*	—	−11	+15
	C_6H_{14}	λ	2068	2569	—
		ε	3000	8200	
		D	+48	+56	
		D*	—	+8	
HO	EtOH	λ	2190	3140	2223
		ε	5500	13,000	8000
		D	+160	+545	+198
		D*	—	+385	+38
	C_6H_{14}	λ	2118	2870	—
		ε	5500	12,000	
		D	+98	+357	
		D*	—	+265	
MeO	EtOH	λ	2195[b]	3050	2223
		ε	7500	13,800	8000
		D	+165	+455	+198
		D*	—	+290	+33
	C_6H_{14}	λ	2198[b]	2920	—
		ε	7000	13,500	
		D	+178	+407	
		D*	—	+229	
HS	EtOH	λ	2375	3175	2425
		ε	8800	12,000	11,000
		D	+345	+580	+403
		D*	—	+235	+58
	C_6H_{14}	λ	2366	3035	—
		ε	7400	14,000	
		D	+346	+522	
		D*	—	+176	
MeS	EtOH	λ	2531	3408[b]	2560[c]
		ε	10,000	14,000	14,000
		D	+501	+813	+535
		D*	—	+312	+34
	C_6H_{14}	λ	2531[d]	3248	—
		ε	9000	15,000	
		D	+511	+735	
		D*	—	+224	
H_2N	EtOH	λ	2344[b]	3725	2444
		ε	8000	16,800	10,000
		D	+314	+1130	+419
		D*	—	+816	+105

[a] L. Doub and J. M. Vandenbelt, *J. Amer. Chem. Soc.* **69**, 2714 (1947).
[b] J. R. Platt and H. B. Klevens, *Tech. Rept.* 1953–1954, Part I. Office of Naval Research.

TABLE 1—*Continued*

X	Solvent		C_6H_5—X ←	p-O_2N—C_6H_4—X ←	p-$H_3\overset{+}{N}$—C_6H_4—X ←
	C_6H_{14}	λ	2340[a]	3203	—
		ε	7500	14,000	
		D	+320	+690	
		D*	—	+370	
O^-	EtOH	λ	2374[a]	4010	—
		ε	12,500	24,000	
		D	+344	+1415	
		D*	—	+1071	
	H_2O	λ	2345[a,c]	3990[f]	—
		ε	11,000	19,000	
		D	+310	+1305	
		D*	—	+995	
S^-	EtOH	λ	2680	4210	—
		ε	14,500	15,000	
		D	+650	+1615	
		D*	—	+965	
	H_2O	λ	2620	4075	—
		ε	12,500	12,000	
		D	+585	+1390	
		D*	—	+805	

D* Increase of displacement by the substituent X as compared with the displacement in the mono-substituted benzene derivatives.

[a] estimated. [b] Fehnel and Carmack[10] give 338 mμ. [c] Fehnel and Carmack[10] give 254 mμ in water. [d] Mangini and Passerini[11] give 254 mμ. [e] Doub and Vandenbelt[6] give 235 mμ. [f] Doub and Vandenbelt[6] give 402·5 mμ.

the O_2N—C system on introduction of the still electron attracting fluorine atom. The former effect is reduced in hexane (D* being only +8 Å) and even reversed in ethanol (D*, −11 Å), since the polarity and the electron attracting power of the C—F group is enhanced in the latter solvent.[3]

The given interpretation is convincingly supported by the fact that the *differences* in the displacements of the K-bands of benzene and nitrobenzene (D*) increase in the order of substituents F (8 Å in hexane; −11 Å in ethanol) $\ll$ SH (176 Å; 235 Å) $<$ OMe (229 Å; 290 Å) $\sim$ SMe (224 Å; 312 Å) $<$ OH (265 Å; 385 Å) $\ll$ NH_2 (370 Å; 816 Å) $<$ S^- (—; 965 Å) $<$ O^- (—; 1071 Å), and that, again except for the fluorine atom (see above), this effect is enhanced in the same order of substituents on replacing hexane by ethanol.

This is in agreement with the general experience, based on well-known studies of physical properties and, in particular, of the rates of chemical reactions and of equilibria, that the electron shifts resulting from an increased electron demand at the carbon atom of a group C—X (in this case, on introduction of the nitro group and on replacement of hexane by ethanol) increase in the given order of substituents X which, except for the hydrogen atom, coincides, on the whole, with their electron repelling character.*

It should be noted, however, that a more quantitative analysis of the differences

* This is commonly attributed to an increasing mesomeric effect in the order given.

[10] E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.* **71**, 2889 (1949).

[11] A. Mangini and R. Passerini, *J. Chem. Soc.* 4954 (1956).

D* would require the consideration of an additional factor which will be discussed in greater detail elsewhere. The degree of stabilisation of the normal excited state, i.e. the red-shift of a K-band, due to the perturbation not only, as is well-known, by a terminal —CH=CH_2 group, but by *any* substituent decreases as the length (or polarisability) of the substituted absorbing system increases. This factor will tend to reduce the greater bathochromic effect of substituents in the *p*-nitrobenzene derivatives as compared with their effect in the benzene derivatives, i.e. the displacements D*. This factor cannot be neglected in an analysis of the significance of the only moderate differences of D* observed for the sulphur and corresponding oxygen containing substituents, for which reason it is not attempted at this stage.

The preceding discussion shows that in the *p*-nitrobenzene derivatives the polarisability of the terminal groups C—X as well as of the substituted system becomes much more closely related to the electron repelling character of the substituents than in the benzene series. This is particularly well illustrated by the observation (1) that, in contrast to the very similar positions of the K-bands of thiophenol, aniline and the phenoxide ion in ethanolic solution (2374 Å; 2344 Å; 2375 Å), those of the corresponding *p*-nitrobenzene derivatives are strongly displaced from 3175 Å to 3725 Å and 4010 Å, i.e. in their order of polarity, and (2) that, whereas thioanisole absorbs at considerably longer wavelengths (2531 Å in ethanol and hexane) than the more polar aniline (2340; 2344 Å), in hexane the difference is considerably reduced for *p*-nitrothioanisole (3248 Å) and *p*-nitroaniline (3203 Å) and in ethanol the latter absorbs even at much longer wavelengths (3725 Å) than the former (3408 Å).

Effect of hydrogen bond formation. The displacements to shorter wavelengths of the K-bands of the phenoxide and thiophenoxide ions on replacing ethanol by the more strongly hydrogen bonding water (29 and 60 Å respectively) are also observed for the corresponding *p*-nitrobenzene derivatives (110 and 225 Å respectively). They are greater, because they include the effect arising from the reduced polarity of the O_2N—C system.

Similarly the contribution of the now increased polarity of the O_2N—C group explains that the displacement of the K-band of *p*-nitrophenol to longer wavelengths due to hydrogen bond formation of the phenolic hydrogen atom with ethanol is greater than that observed for phenol. Whereas in hexane the K-band of *p*-nitroanisole appears at longer wavelengths (by 50 Å) than that of *p*-nitrophenol, in ethanol the reverse is true, the K-band of nitrophenol absorbing at much longer wavelengths (by 90 Å). Thus, the displacement caused by hydrogen bond formation is approximately 140 Å as compared with the 75 Å observed for phenol itself.

Again, the spectrum of *p*-nitrothiophenol in ethanol does not indicate the formation of a hydrogen bond, since the difference between the position of the K-bands of this thiophenol and its methyl ether is even slightly greater in ethanol (233 Å) than in hexane (213 Å). The different tendency of the hydroxyl and thiol groups to form hydrogen bonds accounts for the observation that in ethanol the positions of the K-bands of *p*-nitrophenol and *p*-nitrothiophenol are similar (3140 and 3175 Å respectively), but in hexane are very different (2870 and 3035 Å respectively).

(c) p-*Substituted anilinium ions*

According to Doub and Vandenbelt[8] the maxima of the K-bands of benzene and of the anilinium ion in water appear at 2035 Å and 2030 Å, respectively. The

insignificant displacement to shorter wavelengths on introduction of the $\overset{+}{N}H_3$ group indicates that the electron polarisability of the C—$\overset{+}{N}H_3$ group, similar to that of the C—F group, at least towards the substituent is smaller than that of the C—H bond. Assuming the direction of the effective charge migration is towards the ammonium group (VI), the electron shift (in the ground state) within the phenyl group should have produced a slight displacement of the K-band to longer wavelengths.

$$\xrightarrow{X—C_6H_4—\overset{+}{N}H_3} \quad (X = H, F, OH, OMe, SH, SMe, NH_2)$$

VI

As shown in the third column of Table 1, the introduction of the $\overset{+}{N}H_3$ group into the *para* position of fluorobenzene, phenol, anisole, thiophenol, thioanisole and aniline (VI) displaces the corresponding K-bands moderately to longer wavelengths (D*: 15, 38, 33, 58, 34, 105 Å). This can be attributed to an increased electron shift, particularly within the C—X groups, towards the carbon atom, this shift, as could be expected, being greater than that occurring in the corresponding C—H bond of the anilinium ion itself.

The *increase* of the displacements of the benzene K-band by the OH, OMe, SH, SMe and NH_2 substituents on introduction of the $\overset{+}{N}H_3$ group is much smaller than that observed in the corresponding *p*-nitrobenzene derivatives, which should be attributed to much smaller electron shifts in the $H_3\overset{+}{N}$—C system than in the O_2N—C system. In agreement with this interpretation, the smaller displacement of the K-band of nitrobenzene as compared with that of benzene on introduction of the electron attracting fluorine atom (D*, −11 Å in ethanol) due to the reduced polarity of the O_2N—C group (cf. above) is not observed in the *p*-fluoroanilinium ion (D*, +15 Å).

3. EFFECT AS ELECTRON-ACCEPTING TERMINAL GROUPS OF THE EFFECTIVE ELECTRON MIGRATION

As recently shown,[3] the electronic polarisability of the (aromatic) C—Hal groups is greater towards the carbon atom than in the opposite direction.* Thus, these groups are responsible for much smaller displacements of the K-bands to longer wavelengths and in the case of the C—F group even for displacements to shorter wavelengths, if they are electron-receiving terminal groups of the effective electron migration, e.g. in absorbing systems such as (VII). This is illustrated in Table 2 by a

TABLE 2. DISPLACEMENTS OF K-BANDS (IN Å) IN HEXANE SOLUTION ON INTRODUCTION OF HALOGEN ATOMS

X	$X—C_6H_5$ →	p-$X—C_6H_4—\overset{+}{N}H_3$ ←	p-$X—C_6H_4—OMe$ ←	p-$X—C_6H_4—I$ ←
F	48	−35	−35	−13
Cl	132	73	82	63
Br	140	78	72	90
I	280	123	142	125

* This is in contrast to the reversed order of polarisability in the aliphatic C—Hal groups.[3]

comparison of the displacements observed for the K-bands of the halogenobenzenes with those e.g. observed for the *p*-halogenoanilines, *p*-halogenoanisoles and *p*-halogenoiodobenzenes in hexane solution.

$$\xrightarrow{p\text{-A}-C_6H_4-\text{Hal}} \quad (A = NH_2, OMe, I)$$

VII

The effect of the hydroxyl, methoxyl, mercapto, methylmercapto, amino, and charged oxygen substituents at the receiving end of the effective electron migration (VIII) has now been investigated.

$$\xrightarrow{p\text{-A}-C_6H_4-X} \quad (X = OH, OMe, SH, SMe, NH_2, \text{or } O^-)$$

VIII

The observed maxima of the K-bands of thiophenol, thioanisole, and aniline in hexane and ethanol and of the phenoxide and thiophenoxide ions in ethanol and water (VIII, A = SH, SMe, NH_2, O^- or S^-) as well as their derivatives substituted in *para* position by similar groups (VIII, X) are collected in Table 3. The data have been arranged to show the effect of these substituents at the receiving end of the effective electron migration (the direction of which is indicated by long arrows). The corresponding displacements (D) are also given. A few data illustrating the effect of the fluorine atom, reported earlier,[3] are again added for comparison.

The direction of the effective electron migration corresponding to the observed K-band in these *p*-disubstituted benzene derivatives can be established by a comparative analysis of the displacements of the K-bands on introduction of the various groups (for the corresponding analysis applied to the *p*-substituted halogenobenzenes, cf. reference 3). Thus, the magnitude of the displacements due to an SMe group at the receiving end is 212–214 Å and 194–204 Å in the unambiguous cases of *p*:*p*′-dimethylmercapto-benzene and of the *p*-methylmercapto-thiophenoxide ion respectively. In contrast, the displacements of the K-bands of phenol, thiophenol, anisole, aniline, and the phenoxide ion on introduction of a methylmercapto group into the *p*-position vary between 253 and 452 Å, i.e. the K-band appears at much longer wavelengths than could be expected, if the SMe group would be at the receiving end of the electron migration of the transition.

Similarly, the displacement of the K-band due to the electron accepting terminal amino group in *p*-phenylenediamine, *p*-amino-thioanisole, the *p*-aminophenoxide and *p*-aminothiophenoxide ions varies between 22 and 119 Å, whereas the corresponding displacements in *p*-aminophenol, *p*-aminoanisole, and *p*-aminothiophenol (144–232 Å) are too high for a receiving terminal amino group.

Again, the differences between the position of the K-bands of *p*-hydroxythioanisole, of *p*-hydroxyaniline, and of *p*-hydroxythiophenol and that of the corresponding *p*-methoxy derivatives are small and are of the same order in both hexane and ethanol. The displacements to longer wavelengths due to hydrogen bond formation with ethanol to be expected for phenols, in which the hydroxyl groups are at the electron donating end of the effective electron migration, are not observed. Thus, the hydroxyl and methoxyl groups in these molecules can only be at the receiving end of the effective charge migration.

In Table 4, the observed displacements of the K-bands by the investigated groups at the donating and at the receiving ends respectively of the effective electron migration

TABLE 3. MAXIMA OF K-BANDS OF COMPOUNDS $p\text{—A—}C_6H_4\text{—X} \rightarrow$ IN Å

X	Solvent		A: MeS-	H_2N-	HS-	Me_2N-	S^--	O^--
H	EtOH	λ	2531	2344	2375	—	2680	2374
		ε	10,000	8000	8800		14,500	12,500
	C_6H_{14}	λ	2531	2340	2366	2500[11,a]	—	—
		ε	9000	7500	7400	14,100		
	H_2O	λ	2487	—	—	2440[12]	2620	2345
		ε	10,000			8700	12,500	11,000
F[b]	EtOH	λ	—	2334	—	—	—	2350
		ε		7000				7500
		D		−10				−24
	C_6H_{14}	λ	—	2305	—	—	—	—
		ε		7000				
		D		−35				
	H_2O	λ	—	—	—	—	—	2318
		ε						6000
		D						−27
HO	EtOH	λ	2552[b]	2349	2375	—	—	—
		ε	11,000	9300	8500			
		D	+21	+5	0			
	C_6H_{14}	λ	2570	2350	2346	2470[11,c]	—	—
		ε	7000	8000	8000	11 000		
		D	+39	+10	−20	−30		
MeO	EtOH	λ	2560	2354	2396	—	2665	2390
		ε	10,000	10,500	10,500		16,000	8500
		D	+29	+10	+21		−15	+16
	C_6H_{14}	λ	2568	2370	2368	2500[11,c]	—	—
		ε	9000	10,000	9500	13,500		
		D	+37	+30	+2	0		
	H_2O	λ	—	—	—	—	2620	2352
		ε					14,000	8500
		D					0	+7
HS	EtOH	λ	2695	2520	—	—	—	—
		ε	15,000	14,000				
		D	+164	+176				
	C_6H_{14}	λ	2695	2510	—	—	—	—
		ε	14,500	14,000				
		D	+164	+170				
H_2N	EtOH	λ	2632[d]	2440	—	—	2702	2452
		ε	14,000	11,000			16,000	11,000
		D	+101	+96			+22	+78
	C_6H_{14}	λ	2632[e]	2459	—	2560[11,c]	—	—
		ε	10,000	8500		12,000		
		D	+101	+119		+60		
	H_2O	λ	—	—	—	—	2657	2430
		ε					15,000	10,500
		D					+37	+85
MeS	EtOH	λ	2745	—	—	—	2874	—
		ε	19,500				17,500	
		D	+214				+194	
	C_6H_{14}	λ	2743	—	—	—	—	—
		ε	19,000					
		D	+212					

[12] H. E. Ungnade, *J. Amer. Chem. Soc.* **75**, 432 (1953).

TABLE 3—*continued*

X	Solvent	A: MeS-	H_2N-	HS-	Me_2N-	S^--	O^--
	H_2O	λ — ε D	—	—	—	2824 17,000 +204	—
O^-	EtOH	λ 2627[f] ε 14,500 D +96	—	—	—	—	—
	H_2O	λ 2595[g] ε 15,000 D +108	—	—	2450[11] 11,500 +10	2630 13,000 +10	2402 8500 +57

[a] Solvent, heptane. [b] Fehnel and Carmack[10] give 256 mμ. [c] Solvent, cyclohexane. [d] Fehnel and Carmack[10] give 264 mμ. [e] Mangini and Passerini[11] give 264 mμ. [f] Fehnel and Carmack[10] give 263 mμ. [g] Mangini and Passerini[11] give 259 mμ.

are summarised. They show that, as in the case of the C—Hal groups, the electronic polarisability of the (aromatic) C—OH, C—OMe, C—SH, C—SMe, C—NH_2, and C—O^- groups is much greater towards the carbon atom than in the opposite direction. These groups are responsible for much smaller bathochromic displacements of the K-bands, if they are on the receiving end of the effective charge migration.

Also, it may be noted that the electronic polarisability of the investigated groups C—X increases approximately in the same order of substituents X in both directions. $F < OH < OMe < NH_2 < O^- < SH < SMe$. The displacements of the K-bands by the SH, NH_2, and O^- substituents as donating terminal groups are very similar (345, 314 and 344 Å respectively, in ethanol), because the electron repelling NH_2 and O^- substituents are responsible for electron shifts in the ground state of the substituted

TABLE 4. DISPLACEMENTS OF THE K-BANDS (IN Å) BY SUBSTITUENTS X

X	$X{-}C_6H_5$		(A = SH, SMe, NH_2, O^- or S^-) $X{-}C_6H_4{-}A$	
	EtOH	C_6H_{14}	EtOH or H_2O	C_6H_{14}
F	38	48	−10/−27	−17/−38
HO	160	92	0/27	−20/39
MeO	165	178	−15/29	2/37
H_2N	314	320	22/101	101/119
O^-	344	—	10/96	—
HS	345	346	164/176	164/170
MeS	501	511	194/214	212

phenyl group which coincide with the direction of the effective charge migration of the transition and, thus, make some additional contribution to the bathochromic displacement of the K-band (cf. above). On the other hand, when these groups are on the receiving end, the observed displacements of the K-bands are much smaller for the charged oxygen atom (10–96 Å) and for the amino group (22–101 Å) than for the

mercapto group (164–176 Å) since the electron repelling O^- and NH_2 are now responsible for electron shifts (in the ground state) in the opposite direction to the effective charge migration.

The slight variations of the effect of the investigated groups at the receiving end of the effective charge migration on the position of the K-bands observed in different compounds may arise (1) from the small variations of the polarity of the absorbing systems and, in particular, of the terminal groups, (2) from changes in the degree of perturbation due to differences in the length (or polarisability) of the substituted systems (cf. above), and (3) from small, but varying contributions of the "complementary" charge migration of the transition in the only slightly polar molecules discussed. A detailed analysis and separation of these effects could only be speculative, and it is not attempted.

Table 3 shows also data reported by Ungnade[12] and by Mangini and Passerini[11] for the K-bands of dimethylaniline and of its derivatives containing in the para position a hydroxyl, methoxyl, amino and charged oxygen substituent respectively (IX). The displacements (D) by these substituents (at the receiving end of the effective electron migration of the transition) are, in agreement with those observed in the examples investigated by us, −30, 0, +60 and +10 Å respectively.

$$\xrightarrow{p\text{—}Me_2N\text{—}C_6H_4\text{—}X} \qquad (X = OH, OMe, NH_2, O^-)$$

IX

4. GENERAL CONCLUSIONS

The present investigation confirms the earlier conclusions summarised in the introduction of this paper. Organic molecules are built up of localised bonds only. The constitutive changes of covalent bonds, e.g. the variations of bond energies, interatomic distances and dipole moments, originate in changes of electron repulsions (effective nuclear charges) and involve inductive electron displacements only.

The normal excited state corresponding to a K-band can be described as a "hybrid" of interacting unperturbed states each involving one excited electron, the combined "unperturbed" state involving each electron pair being, for convenience, expressed by one arrow in formula (X). Here, each arrow also indicates the direction of the electron migration (on one side of the nodal plane formed) in phase with the effective charge migration of the observed transition. It should be noted that the total charge migration in this excited state will require the consideration of the "complementary" charge migration as expressed by (XI), but the observed transition energy (position of the K-band) is only to a negligible degree affected by the latter.

Although outside the scope of this paper, the electron migration in the branching electrons of the C—H bonds and (in brackets) the, in absence of any direct experimental evidence, only probable one in the branching non-bonding electrons of the substituents A and B are also indicated (for a general discussion of this matter, cf. reference 4).

The K-band is displaced to longer wavelengths by any structural change which increases the polarisability of the electrons in the absorbing system, i.e. the stability of the corresponding unperturbed excited states, e.g. by a replacement of a bond or group by a more strongly polarisable one or by electron shifts in the ground state coinciding with the effective electron migration of the transition.

X XI

The wave-mechanical resonance characteristic for the electronic perturbations in the excited state of polyelectronic systems represents a physical phenomenon which is absent in the ground state.[4] Thus, the introduction of a substituent possessing an electron affinity similar to the hydrogen atom, e.g. the OMe, SMe, (vinyl or phenyl*) groups in anisole, thioanisole, (styrene or diphenyl) respectively, will be responsible in the *ground state* for only a *negligible* change in the electronic system of the substituted phenyl group, but displace the K-band *strongly* to longer wavelengths as a result of the increased perturbation by the electronic system of the substituent in the *excited state*.

The widely accepted and varying theoretical interpretations of electronic spectra (based on molecular structures involving simplifying concepts such as non-localised bonds, mesomeric electron displacements, a consideration of π electrons only and, in particular, the attempt to build up electronic structures "vertically" with the help of many-centred molecular orbitals by analogy to the building-up principle of atomic structures), again, do not allow for a consistent explanation of the data discussed in this paper.

There is, certainly, no relationship between the (assumed) mesomeric (resonance or delocalisation) effect of the substituents in the ground state particularly of the mono-substituted benzene derivatives and the displacements of the corresponding K-bands to longer wavelengths. As known from studies of physical properties, rates of chemical reactions and chemical equilibria, the former effect, if real, would increase in the order $Me_3C < H_3C < I < Br < Cl < F < SH(SMe) < OH(OMe) < NH_2$, whereas the K-band of benzene is displaced to longer wavelengths (in hexane) in the order $H_3C < F$, $CMe_3 < OH < Cl < Br < OMe < I < NH_2 < SH < SMe$.

What should be even more important, it is difficult to see how any of the theoretical systems involving bond delocalisation can account for the effect of the investigated groups at *the receiving end* of the effective charge migration, e.g. for the much smaller bathochromic and in the case of C—F and, often, of C—OH the hypsochromic band displacements, for the increase of the band displacements in almost the same order of substituents at both the donating and receiving ends of the electron migration (see Table 4), or even for the participation of these groups in the electron migration of the transition. Expressed in valence-bond terminology, contributions from states such as (XII, XIII or XIV) which would contain ten electrons at the halogen, nitrogen or oxygen atoms cannot be seriously contemplated. (cf. also Burawoy and Thompson.[3])

$$\overset{+}{H_2N}=C_6H_4=\overset{-}{Hal} \qquad \overset{+}{H_2N}=C_6H_4=\overset{-}{NH_2} \qquad O=C_6H_4=O^{--}$$

XII XIII XIV

5. EXPERIMENTAL

The spectral determinations were generally carried out with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, a tungsten-steel high tension spark

* The effect of terminal groups containing multiple bonds on K-bands will be discussed in the next part of this series (*Tetrahedron*, in press).

being employed as the source of light. They were in many cases checked with a Hilger Uvispek Photoelectric Spectrophotometer. The spectra of phenol, the *p*-nitrophenolate ion and the *p*-nitrothiophenolate ion were measured by the latter method. Those of the anilinium ions were determined in ethanol and concentrated hydrochloric acid (99 : 1), except for the *p*-aminoanilinium ion the spectrum of which was obtained with a 0·001 M solution of *p*-phenylenediamine in ethanol and 0·4 N aqueous hydrochloric acid (99 : 1). All phenoxide and thiophenoxide ions were measured in 0·3 per cent ethanolic sodium ethoxide and 0·1 N aqueous sodium hydroxide respectively, those of the air-sensitive dibasic salts of hydroquinone and thiohydroquinone in 0·1 N aqueous sodium hydroxide containing 0·1 per cent of sodium bisulphite.

Great care has been taken to obtain the investigated compounds in a high state of purity. All mercaptans were also analysed. Dithiohydroquinone monomethylether has not been previously described.

Dithiohydroquinone monomethylether. *p*-Aminothioanisole (27·8 g) was diazotised by the addition of sodium nitrite (15·5 g), 10 per cent of hydrochloric acid (75 cm³) and sufficient sodium acetate to buffer the solution. The diazonium salt solution was added slowly with vigorous stirring to a solution of potassium ethylxanthate (60 g) in water (40 cm³) kept at 70/80°. Stirring was continued at this temperature for another hour.

The resulting dark-coloured oil was separated and refluxed with potassium hydroxide (23 g), glucose (23 g) and ethanol (400 cm³) for 3 hr. The solution was concentrated to 60 cm³, acidified with dilute sulphuric acid, and the thiol, after addition of zinc dust (3·0 g), steam-distilled. The distillate was extracted with ether, the ether removed after drying over anhydrous sodium sulphate, and the thiol fractionated under reduced pressure, b.p. 116/117°/3 mm, m.p. 29–30°. Yield: 24 g; 80 per cent of theory. (Found: C, 53·8; H, 5·1; S, 41·1. Calc. for $C_7H_8S_2$ C, 54·1; H, 5·2; S, 40·9 per cent).

Dithiohydroquinone dimethylether. A solution of the monomethylether of dithiohydroquinone (10 g) in 40 per cent of aqueous sodium hydroxide (20 cm³) was vigourously stirred while dimethylsulphate (5·0 g) was added. The precipitate of the dimethylether was collected (9·0 g; 83 per cent of theory). It crystallised from light petroleum (b.p. 60–80°) as colourless plates of m.p. 85° (Zincke and Frohneberg[13] obtained it from dithiohydroquinone and give m.p. 85°) (Found; C, 56·4; H, 5·9; S, 37·4. $C_8H_{10}S_2$ requires C, 56·5; H, 5·9; S, 37·6 per cent).

Acknowledgements—We wish to thank Mr. B. Manohin for the microanalysis carried out in connection with this investigation and the Department of Scientific and Industrial Research for a grant to one of us (J. P. C.).

[13] Th. Zincke and W. Frohneberg, *Ber. Dtsch. Chem. Ges.* **42**, 2721 (1909).

Tetrahedron, 1958, Vol. 4, pp. 418–429. Pergamon Press Ltd., London

NOTES

The structure and substitution of the C–D ring system of delphinine

(*Received* 22 *July* 1958)

THE alkaloid delphinine ($C_{33}H_{45}NO_9$) is one of the most complex and most extensively investigated members of the Aconite–Delphinium–Garrya group. Mainly by the efforts of Jacobs[1] it has been shown to possess six rings, a tertiary nitrogen carrying an N-methyl group, an acetoxy, benzoxy and tertiary hydroxy group, and four methoxyls.

We have now derived the partial structure (I) for delphinine on the basis of experimental data of Jacobs[1] (which we have partly repeated and corroborated) as well as on the basis of our own experiments. The same partial formula also represents α-oxodelphinine which is an N-formyl compound. Pyro-α-oxodelphinine is represented by (II) and *iso*pyro-α-oxodelphinine which is obtained from (II) by methanolic HCl is portrayed by the formula (III). The transformation (II → III) is thus a shift of a double bond, with no skeletal rearrangement. The methoxyl in brackets represents the only alternative formulation of the pyro-*iso*pyro reaction, namely an allylic shift.

Hydrolysis of the benzoxy group in (III) gave the corresponding diol which Jacobs[2] oxidised to an α,β-unsaturated keto acid, now represented by (IV). Compound (IV) is easily isomerised[2] to the γ-lactone (V). Dihydro-α-oxo*iso*pyrodelphonine has been oxidised[3] to the corresponding ketone which we now represent by (VI).

Compound (VI) is transformed[3] by the action of alkali into the isomer formulated by us as (VII). Our own experimental evidence (vide infra) is concerned with the proof of this transformation. The reaction (VI → VII) is connected with a characteristic large laevorotatory change ($\Delta[\alpha]_D = -110$). Dihydro (II) may be saponified and oxidised[3] analogously to dihyro-α-oxo-delphonone (VIII) which is a diastereoisomer (and) or methoxyl-position-isomer of (VI). Treatment of (VIII) with alkali gives an isomeric ketone (IX). The reaction (VIII → IX) is accompanied by the same laevorotatory change as the reaction (VI → VII). This is strong evidence for the identical skeletal structure of (II) and (III).

The same series of reactions may also be performed with (I).[3] This gave both in Jacobs'[3] and our hands α-oxodelphonone (X), which may be isomerised by alkali to the *iso*delphonone (XI). The molecular rotational difference of the change (X → XI) is again the same as for the reaction (VI → VII). We have now confirmed the correctness of our formulations in the following manner.

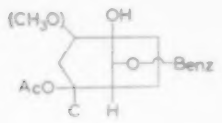
Compound (XI) takes up precisely one mole of periodic acid and gives acidic material which spontaneously on work-up eliminates a molecule of water and gives an acid (m.p. 187°), crystallising with half a mole of ethanol, and formulated as (XII). (Found: C, 61·70; H, 7·58; O, 28·02; N, 3·00; Calc. for $C_{24}H_{33}NO_6 \cdot \frac{1}{2}C_2H_5OH$: C, 61·70; H, 7·46; O, 27·99; N, 2·88%.) The ultra-violet spectrum of (XII) (λ_{max} 257 mμ, log ε = 4·1) indicates a trisubstituted α,β-unsaturated ketone. The infra-red frequency (1710 cm^{-1}) of the conjugated keto group is in agreement with a five-membered ring ketone.

Jacobs[3] has shown that oxidation of (X) with chromium trioxide gives a seco-acid which we now formulate as (XIII). We have also obtained (XIII) by treatment of α-oxodelphonine with periodic acid followed by neutralisation and treatment with permanganate. Compound (XIII) is completely stable to warm aqueous alkali. On the other hand, treatment of the oily methyl ester of (XIII) (I. R. 1706 cm^{-1} ketone, 1736 cm^{-1} ester) with methanolic sodium methoxide at reflux temperature followed by saponification gives the acid (XII) presumably via the diketone (XIV). All the reactions discussed constitute a rigorous proof of the partial formulae used in this communication.

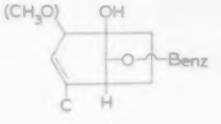
The sequence (XIII → XII) is made possible by the remarkable reluctance of the ester of (XIII) to

[1] For a summarising reference, see W. A. Jacobs and S. W. Pelletier, *J. Amer. Chem. Soc.* **78,** 3542 (1956).
[2] W. A. Jacobs and Y. Sato, *J. Biol. Chem.* **180,** 479 (1949).
[3] W. A. Jacobs and S. W. Pelletier, *J. Org. Chem.* **22,** 1428 (1957).

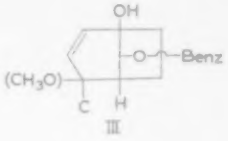
eliminate the β-hydroxyl. This is probably due to the strain of the resulting double bond. A simple explanation of this situation is the assumption that the *cyclo*heptane system in (XIII) is attached to the rest of the molecule by the two carbons "β" to the carboxyl.



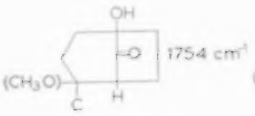
I



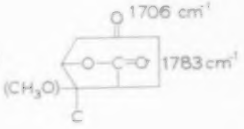
II



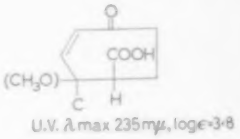
III



VI

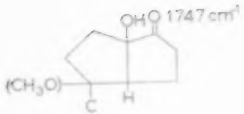


V

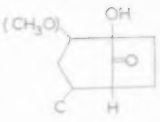


U.V. λ max 235mμ, log ε=3·8

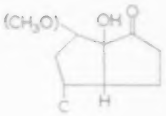
IV



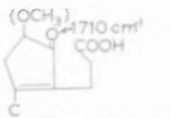
VII



VIII

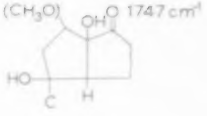


IX

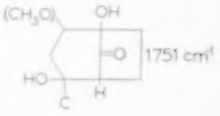


U.V. λ max 257 mμ, log ε=4·1

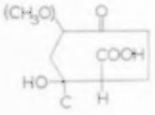
XII



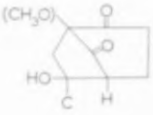
XI



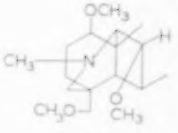
X



XIII



XIV



XV

In this case, of course, even the double bond in (II) is strained. However, consideration of models shows that the strain in (II) is definitely not intolerable. Moreover, (II) is formed by pyrolysis and is isomerised to (III) exceedingly readily.

It is striking that the partial structure of delphinine is a substituted bi*cyclo*(1,2,3)octane system which is the characteristic structural feature of all diterpenoid alkaloids or their biogenetic precursors.[4]

Thus we may assume that the partial structure (I) represents the C–D ring system of a diterpenoid alkaloid. For the rest of the molecule, the demethylation studies of Jacobs[5] are very pertinent. The fact that the A–B system is modified is indicated by a positive outcome of the first stage Hofmann degradation (cf. 3).

[4] Z. Valenta and K. Wiesner, *Chem. & Ind.* 354 (1956).
[5] W. A. Jacobs and S. W. Pelletier, *J. Amer. Chem. Soc.* **76**, 161 (1954).

We consider the partial structure (XV) as a biogenetically plausible, but unproved working hypothesis for the A, B and nitrogen rings of delphinine. This partial formula coincides to some extent with a structure proposal of Jacobs[1] which in turn is based on the typical diterpenoid alkaloid system.[2]

We intend to discuss the merits of (XV) and the complete structure of delphinine in conjunction with some experimental studies now in progress.

K. Wiesner
F. Bickelhaupt*
Z. Valenta

Organic Chemistry Laboratory
University of New Brunswick
Fredericton, Canada

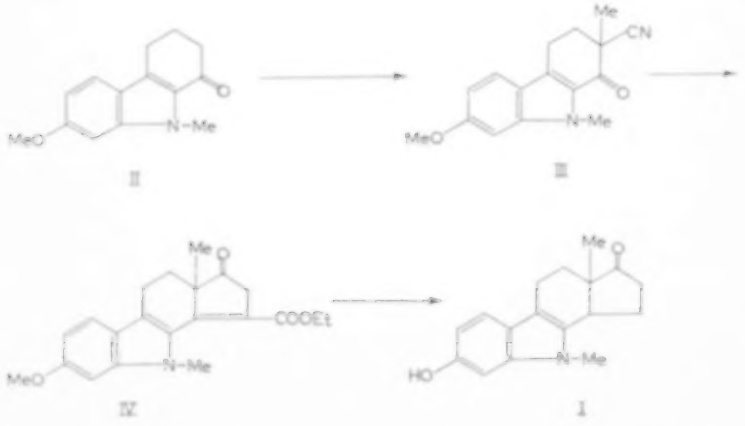
* Holder of an Eli Lilly postdoctoral fellowship.

[1] K. Wiesner, D. R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954); *J. Amer. Chem. Soc.* **76**, 6068 (1954).

Synthesis of 3-Desoxy-B-nor-6-aza-D-homoequilenin

(*Received* 26 *August* 1958)

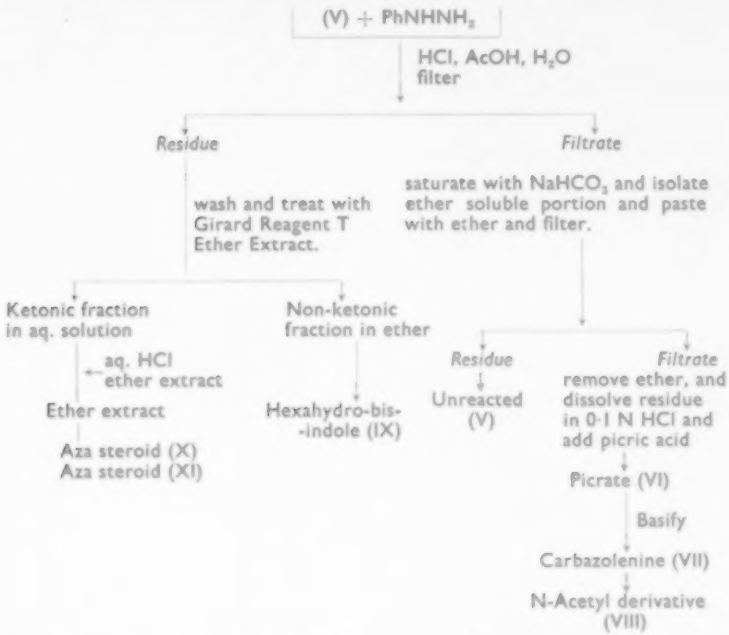
The synthesis of the pyrrolo analogue (I) of equilenin was attempted on the lines of the synthesis of thiopheno[1] and furano[2] steroids reported earlier by us. 7-Methoxy-9-methyl-1-oxo-1:2:3:4-tetrahydrocarbazole (II), m.p. 130°, prepared in three steps from 2- hydroxymethylene*cyclo*hexanone and *m*-methoxybenzenediazonium chloride, was converted into 2-cyano-2:9-dimethyl-7-methoxy-1-oxo-1:2:3:4-tetrahydrocarbazole (III), m.p. 156°, in the usual manner.[1,2] Compound (III), however, could not be converted into the tetracyclic pyrrolo-derivative (IV) by Stobbe condensation with diethyl succinate.



The synthesis of pyrrolo-steroids by an alternative route starting from *trans*-decalin-1:5-dione (V) was then undertaken. The latter (1 mol) and phenylhydrazine (1 mol) were boiled together in acetic

[1] R. B. Mitra and B. D. Tilak, *J. Sci. Industr. Res. India* **15 B**, 573 (1956) *Chem. Abstr.* **51**, 8790 (1957) and earlier papers.
[2] G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Chem. & Ind.* 1319 (1957).

acid for 14 hr followed by addition of hydrochloric acid. The mixture was boiled for a further 5 min, diluted with water, left overnight at 0° and then worked up as shown in the chart:—



The following compounds were isolated as shown in the chart above (analytical values of the compounds are given in Table 1):—*cis*-4:11,2′:3′-(1′-oxo*cyclo*hexano)-1:2:3:4-tetrahydrocarbazolenine (VII), white prisms (petroleum ether, b.p. 40–60°), m.p. 168° (shrinks at 158°). Picrate (VI), yellow needles (acetone), m.p. 197°. Compound (VII) gave the N-acetyl derivative (VIII) [white prisms (petroleum ether b.p. 60–80°), m.p. 136°] and a semicarbazone (VIIIa), white plates (ethanol), m.p. 251°.

The carbazolenine (VII) has been assigned the *cis*-configuration in analogy with the observations of Georgian[3] and on the basis of its facile conversion to compound (VIII) and a study of its Courtauld atomic model.[4]

TABLE 1

Compound No.	Mol. formula	Required %			Found %		
		C	H	N	C	H	N
II	$C_{14}H_{15}NO_2$	73·4	6·5	5·8	73·3	6·8	5·9
III	$C_{16}H_{16}N_2O_2$	71·2	5·5	9·7	71·6	6·0	10·4
VI	$C_{22}H_{20}N_4O_8$	56·4	4·3	12·0	56·7	4·5	12·4
VII	$C_{16}H_{17}NO$	80·3	7·2	5·85	80·7	7·2	5·6
VIII	$C_{18}H_{19}NO_2$	76·8	6·8	5·0	76·6	6·6	4·7
VIIIa	$C_{17}H_{20}N_4O$	68·9	6·8	18·9	68·8	6·8	18·8
IX	$C_{22}H_{20}N_2$	84·6	6·4	9·0	83·9	6·3	9·3
X	$C_{16}H_{17}NO$	80·3	7·2	5·85	80·7	7·6	5·6
XI	$C_{16}H_{15}NO$	81·0	6·4	5·9	80·9	5·6	6·0

[3] V. Georgian, *Chem. & Ind.* 1124 (1957).
[4] R. Robinson, *Disc. Faraday Soc.* **16**, 125 (1954).

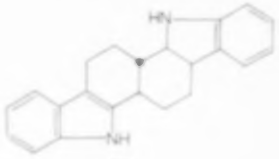
The non-ketonic acid-insoluble fraction yielded 3:4:7:8:9:10-hexahydronaphtho-bis-(1:2-b, 5:6-b′) indole (IX) [pale brown needles (ethanol), m.p. 305–307°] which was isolated through its picrate [dark brown prisms (benzene), m.p. 235–40° (dec.)]. The cyclisation of *cis*- and *trans*-decalin-1:5-dione-diphenylhydrazone has been studied by Hudson and Robinson.[5] Whereas the *cis*-derivative gave a *cis*-bisindole, m.p. 312–316° (dec.), the *trans*-derivative gave an oxygen-containing nitrogeneous compound m.p. 292–96° (dec.) which did not analyse correctly and showed the presence of oxygen.[5]

The acid-insoluble ketonic fraction gave compounds (X) and (XI) which were separated by fractional crystallisation. Compound (XI) was also obtained in the pure form by chromatography on alumina. *Trans*-3-desoxy-B-nor-6-aza-D-homoequilenin (X), m.p. 195°, crystallised in white flakes from methanol. 13:14-Dehydro-3-desoxy-B-nor-6-aza-D-homoequilenin (XI), m.p. 232–35° (softens at 225°), crystallised in yellow prisms from methanol.

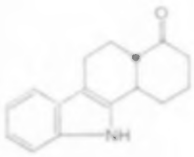
The *trans*-configuration has been assigned to compound (X) in view of its synthesis from compound (V). The structures assigned to compounds (VII), (IX), (X) and (XI) were confirmed by their u.v. spectra and the infra-red spectrum of compound (XI). The spectra were compared with the u.v. and infra-red spectra of 1:2:3:4-tetrahydrocarbazole.

VII

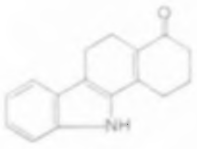
VIII



IX



X



XI

The infra-red spectra of 1:2:3:4-tetrahydrocarbazole and compounds (VII) and (XI) were determined in Nujol mull and the ultra-violet spectra were determined in ethanol solution. The principal absorption maxima and minima are as follows:—

1:2:3:4-Tetrahydrocarbazole

λ_{max} : 228, 283, 338 mμ (log ε = 4·520, 3·820, 0·290)
λ_{min} : 250, 336 mμ (log ε = 3·290, 0·282)
Infra-red absorption bands:—3420, 2940, 1460, 1365, 1330, 1308 cm^{-1}.

Carbazolenine (VII)

(cf. Witkop and Patrick,[6] and Georgian[3])
λ_{max} 259 mμ (log ε = 3·703)
λ_{min} 238 mμ (log ε = 3·505)
Infra-red absorption bands:—2890, 1720, 1590, 1460–1407, 1380, 1240, 1184–1191, 1125, 1030, 907, 775, 758, 752 cm^{-1}.

Hexahydro-bis-indole (IX)

λ_{max} 232, 284, 334 mμ (log ε = 4·863, 4·259, 2·465)
λ_{min} 252, 328 mμ (log ε = 3·851, 2·335)

[5] B. J. F. Hudson and R. Robinson, *J. Chem. Soc.* 691 (1942).
[6] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.* **73**, 1558 (1951).

Aza-steroid (X)

λ_{max} 225, 284 mμ (log ε = 4·528, 3·938)
λ_{min} 250 mμ (log ε = 3·534)

Aza-steroid (XI)

λ_{max} 255, 393 mμ (log ε = 4·041, 4·2492)
λ_{min} 235, 290 mμ (log ε = 3·996, 3·218)

Infra-red absorption bands:—3300, 2930, 1630, 1530, 1455, 1360, 1295, 1190 cm^{-1}.

Starting from compound(V) and *m*-methoxyphenylhydrazine, a synthesis of the desired 3-oxy-derivative of compound (X) appears possible although problems in isomer separation will then arise. Although the above synthesis leads to several reaction products, it is nevertheless of interest in view of the fact that a complex steroidal skeleton is built up in one step starting from readily accessible intermediates.

It is hoped that a detailed account of the work will be published in *Tetrahedron* in the near future.

Department of Chemical Technology
University of Bombay
Bombay, India

G. V. Bhide
N. R. Pai
N. L. Tikotkar
B. D. Tilak

VOL. 4 1958

The hydration heat of the benzenesulphonate ion

(*Received* 27 *August* 1958)

One mole of a solid salt MX may be directly dissolved in excess of water to form hydrated ions, when the enthalpy change is equal to the total heat of solution S; alternatively it may first be split up into gaseous ions, with enthalpy change U equal to the lattice energy, and the ions then hydrated, with enthalpy change H. It follows that

$$S = U + H, \tag{1}$$

and the hydration heat of the pair of gaseous ions M^+ and X^- may be derived if values of U and S are known. Although only hydration heats of pairs of ions may be determined experimentally, it is possible to split up the hydration heats of a pair into the separate contributions of cation, W_{M^+}, and anion, W_{X^-}:

$$H = -(W_{M^+} + W_{X^-}) \tag{2}$$

This problem has been studied by a number of investigators, who have produced consistent values for a number of monatomic ions. Individual ion hydration heats due to Latimer *et al.*[1] and due to Verwey[2] are shown in Table 1.

Table 1. Hydration heats of ions, kcal/g ion

Ion	Li^+	Na^+	K^+	Rb^+	Cs^+	F^-	Cl^-	Br^-	I^-
Latimer *et al.*[1]	121·2	94·6	75·8	69·2	62·0	122·6	88·7	81·4	72·1
Verwey[2]	120	94·5	75	69	61	122	89·5	83	73·5

In the case of an unsymmetrical polyatomic anion such as benzenesulphonate, the hydration heat W_{X^-} cannot be derived from equations (1) and (2), since the lattice energy of a crystalline

[1] W. M. Latimer, K. S. Pitzer, and C. M. Slansky, *J. Chem. Phys.* **7**, 108 (1939).
[2] E. J. W. Verwey, *Rec. Trav. Chim. Pays-Bas* **61**, 127 (1942).

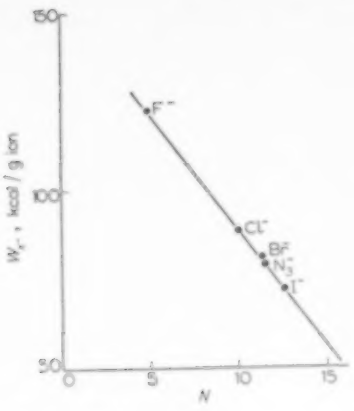


FIG. 1. Relationship between hydration heat of anions and lyotropic numbers.

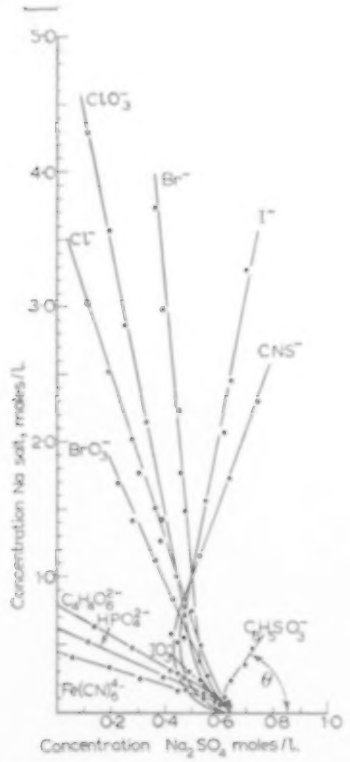


FIG. 2. Concentrations of different sodium salts plotted against concentrations of sodium sulphate, mixtures of which are necessary to bring about flocculation of gelatin sols (Buchner and Postma[9]).

compound such as an alkali benzenesulphonate cannot be computed accurately (for example, it would be necessary to know the Madelung constant for the crystal structure, and the charge distribution of the polyatomic anion).

However, an empirical correlation between anion hydration heat and lyotropic number has been observed and substantiated.[2–5] The lyotropic number, developed by Buchner *et al.*[6–8] is a quantitative expression of the position of an anion in the lyotropic (Hofmeister) series. When known hydration heats of anions are plotted against the corresponding lyotropic numbers, a linear relationship is observed (Fig. 1). If the lyotropic numbe: of the benzenesulphonate ion can be obtained therefore, the hydration heat of the ion may be determined by interpolation.

The lyotropic number of the benzenesulphonate ion can be derived from the graph due to Buchner and Postma[9] on the flocculation of gelatin sols (Fig. 2). If θ is the angle between the line for $C_6H_5SO_3^-$ and the abscissa, then

$$N = 4{\cdot}76 \cot \theta + 11{\cdot}55 \qquad (3)$$

From the measurement of θ it can be calculated that $N = 14{\cdot}95$, and by interpolation in Fig. 1 it follows that the heat of hydration of the benzenesulphonate ion $W_{\mathrm{I}}^- = 56{\cdot}4$ kcal/g ion (298°K).

The procedure illustrated here appears to be the only possible one available at present for the accurate derivation of the hydration heats of various unsymmetrical polyatomic anions.

New College,
University of Oxford

D. F. C. Morris

[3] A. Voet, *Chem. Rev.* **20**, 169 (1937).
[4] P. Gray and T. C. Waddington, *Proc. Roy. Soc.* A **235**, 481 (1956).
[5] D. F. C. Morris, *J. Inorg. Nucl. Chem.* **6**, 295 (1958).
[6] E. M. Bruins, *Proc. Acad. Sci. Amsterdam* **35**, 107 (1932).
[7] E. H. Buchner, A. Voet, and E. M. Bruins, *Proc. Acad. Sci. Amsterdam* **35**, 563 (1932).
[8] E. H. Buchner, E. M. Bruins, and J. H. C. Merckel, *Proc. Acad. Sci. Amsterdam* **35**, 569 (1932).
[9] E. H. Buchner and G. Postma, *Proc. Acad. Sci. Amsterdam* **34**, 699 (1931).

Synthesis of methyl 2-acetamido-2-deoxy-β-D-glucofuranoside

(*Received* 15 *September* 1958)

Despite the wide distribution of glucosamine in natural products, the ring form and mode of linkage is known only in a few cases and in these, only the pyranose modification has so far been found.[1–3]

The stability which many polysaccharides containing glucosamine show towards acidic hydrolysis is consistent with the behaviour of known pyranosides of glucosamine under identical conditions[4,5] and this is often taken as evidence of the predominance of pyranose form of the amino-sugar in polysaccharide chains.

It is now of interest to examine the stability of furanoside derivatives of glucosamine with a view to assessing the contribution that this form of the amino-sugar may make in polysaccharide structures, particularly as potential sites of acid-labile linkages.

The failure of glucosamine to form glycosides with methanolic hydrogen chloride has led to the investigation of an alternative synthesis via the neutral scission of the sugar mercaptal. Wolfrom *et al.*[6] synthesised a methyl β-thioglycoside of glucosamine and by an analogous route we have now obtained in a crystalline form methyl 2-acetamido-2-deoxy-β-D-glucofuranoside from N-acetyl

[1] Stacey and Woolley, *J. Chem. Soc.* 184 (1940).
[2] Haworth, Kent and Stacey, *J. Chem. Soc.* 1211 (1948).
[3] Kent and Whitehouse, *Biochemistry of Aminosugars*. Butterworths, London (1955).
[4] Moggridge and Neuberger, *J. Chem. Soc.* 745 (1938).
[5] Foster, *J. Chem. Soc.* 1817 (1958).
[6] Wolfrom, Olin and Polglase, *J. Amer. Chem. Soc.* **72**, 1724 (1950).

D-glucosamine diethylthioacetal[7,8] by the action of mercuric oxide in methanol.[9] The N-benzyloxycarbonyl-furanoside was obtained in the same way from the appropriately N-substituted mercaptal.

The structure of the new glucoaminides has been assigned on the basis of the following evidence:—

(i) The glycosides were hydrolysed rapidly by mineral acids (0·04 N·H^+) with the formation of N-acetyl and N-benzyloxycarbonyl glucosamine respectively. Under identical conditions the corresponding pyranosides were not hydrolysed.

(ii) In the course of hydrolysis, the optical rotation became more dextrorotatory and the glycoside was provisionally designated a β-configuration.

(iii) A series of comparative oxidations was performed simultaneously on the new methyl N-acetyl, and methyl N-benzyloxycarbonyl-β-furanosides and the corresponding pyranosides (methyl N-acetyl-β-glucosaminide, methyl N-benzyloxycarbonyl-α-glucosaminide) N-benzyloxycarbonyl-glucosamine and N-acetylglucosamine. The oxidation with periodate ion was non-stoicheiometrical and in the case of the furanosides was shown to be accompanied in the early stages by the liberation of formaldehyde which is consistent with the presence of a terminal glycol group. In contrast to the pyranoside glycosides, the furanosides were oxidised rapidly by lead tetracetate, one mole of oxidising agent being consumed by one mole of the methyl N-benzyloxycarbonyl furanoside in 6 hr. In the same time, 1 mole of the authentic N-benzyloxycarbonyl pyranoside consumed only 0·3 mole of lead tetracetate. The N-acetyl furanoside was oxidised under identical conditions at a much faster rate than methyl 2-acetamido-2-deoxy-β-D-glucopyranoside.

(iv) The new N-acetyl and N-benzyloxycarbonyl methyl furanosides were methylated with methyl sulphate and sodium hydroxide. Only after acetylation[10] were products obtained containing the calculated methoxyl content for fully etherified substances. Without acetylation, only 90 per cent substitution was effected. The N-substitutent was removed from the fully methylated N-benzyloxycarbonyl furanoside by catalytic hydrogenation and the glycosidic group cleared by hot aqueous acid. In the absence of an N-substitutent, the glycoside was more resistant to hydrolysis and this is in agreement with the findings of Moggridge and Neuberger.[4] The resulting trimethyl glucosamine, formed a crystalline phenylosazone indistinguishable from authentic 3:5:6-trimethyl-D-glucosazone (X-ray powder photograph). Oxidation of trimethyl glucosamine with sodium metaperiodate or ninhydrin yielded a non-crystalline trimethyl pentose chromatographically identical with 2:4:5-trimethyl-D-arabinose.[11]

The new N-acetyl furanoside gave no indication of alkali sensitivity though it gave a weakly positive Elson and Morgan test.

EXPERIMENTAL

C.H.N. analyses were carried out by Drs. Strauss and Weiler (Oxford). Chromatographic examinations were performed on Whatman No. 1 paper with butanol-ethanol-water (4 : 1 : 5) as the elution system, and the sugars revealed with aniline hydrogen phthalate or iodine vapour.

Methyl 2-acetamido-2-deoxy-β-D-glucofuranoside (I)

N-acetyl D-glucosaminediethylthioacetal (5 g) prepared by the method of Whitehouse *et al.*[11] was shaken for 6 hr with mercuric oxide (6·7 g) and mercuric chloride (8·3 g) in dry methanol (50 ml). After heating to 55° for 35 min, the filtered solution was shaken with metallic mercury for 5 days. The inorganic material was separated centrifugally and the supernatant solution evaporated, giving a syrup which crystallised spontaneously. The product, recrystallised from *iso*propanol, had m.p. 193° $[\alpha]_D^{18}$ −20° (*c*, 0·6 in H_2O), R_F 0·31. (Found: C, 42·5; H, 7·33; N, 5·0; OMe, 13·6; $C_9H_{17}O_6$ requires: C, 46·0; H, 7·24; N, 5·95; OMe, 13·2%).

Neuberger and Pitt-Rivers[12] report m.p. 196°, $[\alpha]_D$ −43° (H_2O) for methyl 2-acetamido-2-deoxy-β-D-glucopyranoside.

[7] Kent, *Research* **3**, 427 (1950).
[8] Wolfrom, Lemieux and Olin, *J. Amer. Chem. Soc.* **71**, 2870 (1949).
[9] Green and Pacsu, *J. Amer. Chem. Soc.* **59**, 1205, 2569 (1937).
[10] Cutler, Haworth and Peat, *J. Chem. Soc.* 1979 (1937).
[11] Whitehouse, Kent and Pasternak, *J. Chem. Soc.* 2315 (1954).
[12] Hockett and McClenahan, *J. Amer. Chem. Soc.* **61**, 1667 (1939).
[13] Bergman and Zervas, *Ber. dtsch. Chem. Ges.* **65**, 1192 (1932).
[14] Neuberger and Pitt-Rivers, *J. Chem. Soc.* 122 (1939).

Methyl 2-benzyloxycarbonylamino-2-deoxy-β-D-glucofuranoside (II)

N-Benzyloxycarbonyl-D-glucosaminediethylthioacetal (5 g) was dissolved in dry methanol (50 ml) and treated with freshly prepared yellow mercuric oxide (5·5 g) and mercuric chloride (6·25 g) at 37° for 12 hr. A syrupy product was isolated in the above manner, yield 3 g, n_D^{25} 1·5201, $[\alpha]_D^{19}$ −38° (*c*, 0·12 in EtOH), $[\alpha]_D^{22}$ −16° (*c*, 0·65 in H_2O), R_F 0·88 (Found: OMe, 9·7; $C_{15}H_{21}O_7N$ requires: OMe 9·5%).

Acidic hydrolysis of N-*substituted methyl*-D-*glucosaminides*

(i) The N-acetyl-furanoside (I, 120 mg) was heated with sulphuric acid (0·04 N, 25 ml) on a boiling water-bath.

Time (hr)	0	0·5	1	3	6
$[\alpha]_D^{22}$	−20°	+4	+12·5	+30	+41·5

The hydrolysate, which reduced Fehlings solution, was neutralised with barium carbonate and filtered, yielding on evaporation a reducing sugar $[\alpha]_D^{18}$ +44° (H_2O, *c*, 0·48) R_F 0·23. N-acetyl-D-glucosamine shows $[\alpha]_D^{18}$ +42; R_F 0·24. (Authentic methyl 2-acetamido-2-deoxy-β-D-glucopyranoside under identical conditions showed $[\alpha]_D^{22}$ −37 → +31° in 6 hr.)

(ii) N-Benzyloxycarbonyl-furanoside (III, 120 mg) in sulphuric acid (0·04 N, 25 ml) was heated at 100°.

Time (hr)	0	0·5	1·0	2
$[\alpha]_D^{18}$	−15·5	+11·5	+23	+27

The hydrolysate, neutralised with barium carbonate, filtered and evaporated, yielded crystalline N-benzyloxycarbonyl-glucosamine, m.p. 200°, (decomp) chromatographically identical with an authentic specimen.

Authentic methyl 2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside treated with identical reagents was not hydrolysed after 6 hr.

Oxidations with lead tetra-acetate[13]

50–100 mg of glycoside was dissolved in 100 ml of 10% acetic anhydride glacial acetic acid containing 0·77 g lead tetra-acetate. At intervals, 5 ml aliquots were withdrawn, transferred into 10 ml of an iodide buffer (20 g potassium iodide and 250 g anhydrous sodium acetate in 1 l. solution) and the iodine liberated was titrated with 0·02 N sodium thiosulphate. A control consisting of lead tetra-acetate alone was maintained under identical conditions.

(i) *Methyl 2-acetamido-2-deoxy-β-D-glucofuranoside* (I, 57 mg)

Time (hr)	1	2·5	7·5	8·5
$Pb(OAc)_4$ consumed (mole/mole)	0·11	0·22	0·33	0·66

(ii) *Methyl 2-benzyloxycarbonylamino-2-deoxy-β-D-glucofuranoside* (II, 44 mg)

Time (hr)	1	2	3	4	11	22	34	58	82
$Pb(OAc)_4$ consumed (mole/mole)	0·31	0·62	0·80	0·83	0·88	0·92	1·12	1·65	1·80

The presence of formaldehyde (detected by chromatropic acid) and another aldehyde (chromatography) was demonstrated after 12 hr. No N-acetylglucosamine was detected.

(iii) *Methyl N-benzloxycarbonylamino-2-deoxy-α-D-glucopyranoside* (70 mg)

Time (hr)	1	2	3	4	11	22	34	46	58	70
$Pb(OAc)_4$ consumed (mole/mole)	0·05	0·10	0·16	0·23	0·33	0·37	0·55	0·68	0·75	0·80

No formaldehyde was detectable.

(iv) *Methyl 2-acetamido-2-deoxy-β-D-glucopyranoside* (56·8 mg)

Time (hr)	1	7·5	20	32
$Pb(OAc)_4$ consumed (mole/mole)	0·01	0·02	0·04	0·05

(v) *N-benzyloxycarbonyl-D-glucosamine* (50·8 mg)

Time (hr)	1	2	3	4	11	22	34	46	58
$Pb(OAc)_4$ consumed (mole/mole)	0·09	0·16	0·21	0·25	0·38	0·78	1·30	1·68	2·26

(vi) *N-acetyl-D-glucosamine* (38 mg)

Time (hr)	1	2	3	4	11	22	34	46	58
$Pb(OAc)_4$ consumed (mole/mole)	0·04	0·07	0·11	0·15	0·16	0·17	0·23	0·25	0·26

Methylation of 2-benzyloxycarbonylamino-2-deoxy-β-D-glucofuranoside (III)

The glycoside (III, 1·8 g) was acetylated with pyridine (10 ml) and acetic anhydride (4·5 ml) at room temp. After two days, the reaction mixture was poured into ice-water and the oily product extracted with ether and washed with water. After drying, the solvent was removed and the acetylated glycoside (n_D^{22} 1·4930, OMe 6·54% 2·2 g), dissolved in chloroform (20 ml), was treated with dimethyl sulphate (30 ml) and sodium hydroxide (30%, 90 ml) added at 45° over a period of 4 hr with continuous stirring. The reaction mixture was stirred for a further 4 hr, saturated with CO_2 and heated on a boiling water bath for 10 min. The cooled solution was neutralised (pH 7·2) with H_2SO_4 and the product separated by repeated extraction with chloroform. The dried extracts were evaporated giving a syrup (1·4 g), OMe, 20·6%.

This product was subjected to remethylation three times by the same procedure. The final product had R_F 0·94 and OMe, 31·6%. The fully methylated derivative requires OMe, 33·6%.

Hydrogenolysis of fully methylated N-*benzyloxycarbonyl-amino furanoside* (IV)

0·6 g of the glycoside in acetone (10 ml) was shaken with freshly prepared palladium black (0·5 g) in a slow stream of hydrogen.[14,15] After 3 hr when no further CO_2 was evolved, the solution was filtered and evaporated to a syrup $[\alpha]_D^{21}$ −32° MeOH, *c*, 1·2, R_F 0·76. (Found: OMe 39·8; $C_{11}H_{21}O_7N$ (amine carbonate) requires: OMe, 40·4%.)

3:5:6-*trimethyl*-D-*glucosamine hydrochloride* (V)

The above free amino glycoside was not hydrolysed readily by 0·04 N mineral acid, but at 100°, the glycosidic group was removed by 1·5 N HCl, $[\alpha]_D^{16}$ −25 → +31 (12 hr).

The product which reduced Fehlings solution, was extracted by chloroform from the reaction mixture which had been made alkaline (pH 8·5) with NaOH. The extracts were dried over anhydrous sodium carbonate and concentrated to a syrup n_D^{17} 1·4645; R_F 0·65, (Found: OMe, 38·8. $C_9H_{19}O_5N$ (free amine) requires: OMe, 40·2%.)

Isolation of 3:5:6-*trimethyl*-D-*glucosazone*

3:5:6-trimethyl glucosamine (V, 30 mg) was dissolved in water (2 ml) containing sodium acetate (0·2 g) and phenylhydrazine (70 mg) and the solution was heated on a boiling water bath for 2·5 hr. After filtration, the solution was evaporated under reduced pressure to a syrup and the product extracted with ethanol. To this a little water was added and a crystalline product separated m.p. 55–57°, which had an X-ray powder diagram identical with that of authentic 3:5:6-trimethyl D-glucosazone.[16] (The authentic material, crystallised once from aqueous ethanol had m.p. 56–58°.)

Oxidation of 3:5:6-*trimethyl*-D-*glucosamine*

A solution of the trimethyl sugar (5 mg) in acetone was added to an aqueous solution of ninhydrin (0·1 g in 10 ml) containing a little sodium bicarbonate. The solution heated on a boiling water bath acquired the characteristic purple coloration and then a brown precipitate was formed which was removed centrifugally after 1½ hr. The solution was concentrated and chromatographed. A substance having the same R_G value (0·96) as 2:4:5-trimethyl-D-arabinose[16] (VII) was found.

Department of Biochemistry
University of Oxford

M. W. Whitehouse
P. W. Kent

[14] Anderson, Charlton and Haworth, *J. Chem. Soc.* 1329 (1929).
[15] Kent and Whitehouse, *J. Chem. Soc.* 2501 (1953).

Tetrahedron, 1958, Vol. 4, pp. 430–431. Pergamon Press Ltd., London

BOOK REVIEWS

"AnalaR" Standards for Laboratory Chemicals, 5th Revised Edition. The British Drug Houses Ltd., Poole and Hopkins and Williams Ltd., Chadwell Heath, 1957. xvi + 397.

THE majority of chemists in the United Kingdom, and many elsewhere, depend on "AnalaR" materials for many of their needs of pure chemicals, and it is therefore invaluable to have the up to date specifications which are given in this book.

There are approximately 290 entries which give the name, formula and molecular weight of the substance and a list of the maximum limits of impurities. To this extent the information is the same as is printed on the label. There follows, however, for each entry a description of the substance and of the tests which are carried out on each batch; this provides a valuable background to the list of possible impurities.

There are seven appendices describing the reagents used in the tests and some of the methods, such as the tests for water and arsenic, electro-deposition of metals, polarographic tests and the method of cation exchange.

Since the last edition of this book in 1949 there have been fourteen additions and twelve deletions. The former include aluminium, ethylenediaminetetra-acetic acid disodium salt, toluene, and xylene, while among the deletions are benzidine, dimethyl yellow, 3:5 dinitrobenzoyl chloride, diphenylbenzidine and some acid-base indicators.

It is gratifying to find that in some of the specifications maximum limits are given for a greater number of impurities than hitherto. Thus the limits for magnesium are given for calcium carbonate and calcium chloride. It is a pity that no information is given about the bromide content of "AnalaR" hydrochloric acid, potassium chloride or sodium chloride; a possible impurity which must often have interested electrochemists.

Altogether this book will be most interesting to all analytical chemists and to those, in many branches of science, doing research which requires the use of pure reagents. Many will be astonished at the wealth of information given in these specifications, some will be more interested in the omissions.

S. P. DATTA

H. v. EULER und B. EISTERT: **Chemie und Biochemie der Reduktone und Reduktonate.** Ferdinand Enke Verlag, Stuttgart, 1957, xi + 344 Seiten, mit 11 Abbildungen und 23 Tabellen. DM 47, 40.

WENIG beachtet von der Mehrzahl der Chemiker ist in den letzten 25 Jahren das Gebiet der Reduktone herangewachsen. Ähnlich den Carbonsäuren haben sie eine zusammengesetzte funktionelle Gruppe, die aus zwei Hydroxylen an den Enden einer Kohlenstoff-Doppelbindung besteht und meist noch mit einer Carbonylgruppe konjugiert ist. Die Einzelfunktionen gehen in dieser Gemeinschaft auf; sie geben viele der üblichen chemischen Reaktionen nicht mehr. Dafür findet man neue. Die Reduktone sind Säuren und starke Reduktionsmittel. Sie sind mit Hydroxycarbonylverbindungen teils tautomer und teils isomer und dann durch Umlagerung daraus zu erhalten. Es ergeben sich enge Beziehungen zu einigen Polyphenolen. Die Hydroxylgruppen können durch Amino- oder Thiolgruppen ersetzt sein. Reduktonate sind die Salze ungesättigter Diole, die aus Acyloinen unter der Einwirkung von Laugen entstehen und ebenfalls Reduktionsmittel sind, aber nur in alkalischer Lösung. Auf das Gemeinsame im Verhalten dieser Stoffe hat zuerst H. v. Euler hingewiesen, der den Namen Reduktone geprägt und vor 8 Jahren mit H. Hasselquist eine kleine Monographie darüber verfasst hat. Daraus ist nun unter massgeblicher Beteiligung von B. Eistert ein stattliches Buch geworden, das alles zusammenträgt und sichtet, was im ganzen Bereich

der organischen Chemie bis 1957 hierüber bekannt geworden ist. Mit Recht ist auch die Biochemie mit in den Titel aufgenommen worden. Sie steht am Anfang der ganzen Entwicklung, denn die Suche nach dem Vitamin C hat ja seinerzeit den Anstoss dazu gegeben. Heute beginnt sich die allgemeine Verbreitung von Reduktonen in Pflanzen und Tieren abzuzeichnen. Es wäre merkwürdig, wenn Stoffe mit solcher Reaktionsfähigkeit nicht noch weitere biochemische Funktionen haben sollten als die bisher von der Ascorbinsäure und dem Bewegungshormon der Mimose her bekannten. Indessen ist es doch wohl das Hauptverdienst des vorliegenden Buches, unter dem Gesichtspunkt der heutigen Vorstellungen in der organischen Chemie das gesamte weitverstreute Tatsachenmaterial einschliesslich Gewinnung, Synthesen, Reaktionen und analytischen Methoden gesammelt und übersichtlich dargestellt zu haben. Das erschöpfende Literaturverzeichnis und manche private Mitteilung, um die sich die Autoren bemüht haben, muss besonders erwähnt werden. Man wird finden, dass kaum ein Bereich der organischen Chemie ohne Beziehung zu diesen Stoffen ist; manche alte Beobachtung erscheint nun in einem neuen Lichte und es dürfte sowohl für die theoretische organische Chemie wie auch für die Untersuchung von Naturstoffen ein starker Impuls davon ausgehen.

G. Hesse

Progress in Stereochemistry. Volume 2. Edited by W. Klyne and P. B. D. de la Mare. Butterworths Scientific Publications, London, and Academic Press Inc., New York, 1958. vii + 323 pp. £2. 10s., $8.80.

The success of Volume 1 in this series, which was published in 1954, has encouraged the preparation of this second volume. The literature in the topics dealt with is covered up to the end of 1956 and some references are given to papers that appeared in 1957.

The use of X-ray analysis and other methods of crystallography in the determination of chemical structures is discussed by J. C. Speakman, with particular reference to the type of compound to which this approach is applicable and the difficulties encountered in practice. This chapter succeeds admirably in giving a clear idea of the problems involved in what, to many chemists, is a difficult and very specialized subject.

The stereochemistry of the free radicals involved in homolytic processes is described by Gareth H. Williams and the stereochemistry of displacements at unsaturated centres by P. B. D. de la Mare. The latter chapter is concerned mainly with aromatic displacements, though some consideration is given to displacements at vinylic centres. There is an excellent chapter by B. M. Wepster on the steric effects of mesomerism, which illustrates the value of such physico-chemical methods as spectroscopy, dipole-moment measurements, dissociation-constant measurements and the study of reaction rates in the elucidation of structures.

Recent work on optically labile compounds is described by M. M. Harris and that on the stereochemistry of the Group V B elements by F. G. Mann. For the biochemist there is an excellent review by J. R. Marrack and Eva S. Orlans on steric factors in immunochemistry, which covers the last decade. In this period the classical work of Landsteiner and others has been extended and refined in the light of newer knowledge of many naturally occurring substances and the greater insight into biochemical mechanisms. In the last chapter R. J. Gillespie and R. S. Nyholm, writing on the stereochemistry or inorganic molecules and complex ions, combine the substance of two recent reviews, one by the same authors on inorganic stereochemsitry and the second on ligand-field theory by J. S. Griffith and L. E. Orgel [*Quart. Rev. Chem. Soc.* **11**, 381, 395 (1957)].

The various chapters are all very clearly and concisely written and will make most interesting and stimulating reading to all practising chemists, and to others working in related sciences, who may well be astonished how much stereochemistry has advanced since the time they learnt about the tartaric acids. The printing and presentation are both very pleasing and there is a commendable lack of errors, albeit there is a remarkable piece of alchemy in reaction 10 on page 91.

S. P. Datta

Papers to be published in future issues

F. LAMB and H. SUSCHITZKY: Studies in the xanthone series—III. Preparation and reactions of 1-acetyl-2-hydroxyxanthone.

A. QUILICO, F. PIOZZI, M. PAVAN and E. MANTICA: The structure of periplanetin.

F. SONDHEIMER and Y. KLIBANSKY: Synthesis of 3β-hydroxy analogues of steroidal hormones, a biologically active class of compounds.

P. MIROSEVIC-SORGO and B. C. SAUNDERS: Toxic fluorine compounds containing the C-F link—X. Rupture of the C-F link by alkali and other reagents.

R. B. WOODWARD and T. J. KATZ: The mechanism of the Diels–Alder reaction.

K. BALENOVIĆ and N. BREGANT: Absolute configuration of α-methyl-β-alanine.

L. PENTIMALLI: Researches on the aromatic compound. The oxidation of the 4-dimethylamine-azobenzene.

SHIGEHIKO SUGASAWA and S. USHIODA: Extension of the Bischler–Napieralski reaction—II. Synthesis of pyrroline derivatives.

W. VON E. DOERING and M. J. GOLDSTEIN: An unusual rearrangement of an acyl oxide.

J. W. CORNFORTH, R. H. CORNFORTH, A. PELTER, M. G. HORNING and G. POPJÁK: Studies on biosynthesis of cholesterol—VII. Rearrangement of methyl groups during enzymic cyclisation of squalene.

A. BURAWOY and J. P. CRITCHLEY: Electronic spectra of organic molecules and their interpretation—V. Effect of terminal groups containing multiple bonds on the K-bands of conjugated systems.

E. M. KOSOWER and D. C. REMY: The effect of a positive charge on a π-π^* transition.

NOBOU ITOH and SHIGEHIKO SUGASAWA: Bischler–Napieralski reaction—III. Synthesis of some ketonic *iso*quinolenes.

J. M. TEDDER and G. THEAKER: The direct introduction of the diazonium group into aromatic nuclei—VI. Reaction mechanisms.

W. D. HOFFMAN, W. E. MCEWEN and J. KLEINBERG: Anodic reductions—V. The reduction of diketones by unipositive magnesium anodically generated.

N. B. DESAI and K. VENKATARAMAN: Raney nickel reductions—VIII. A synthesis of 1:2-benzanthracene and its 3′-methyl and 4′-methyl derivatives.

C. G. MOORE and M. PORTER: The reaction of sulphur and sulphur compounds with olefinic substances—VIII. The mechanism of interaction of sulphur with (+)-limonene.

G. W. K. CAVILL, P. S. CLEZY, J. R. TETAZ and R. L. WERNER: The chemistry of mould metabolites—III. Structure of cinnabarin (polystictin).

R. E. WESTON, JR.: The magnitude of electronic isotope effects.

M. NEEMAN, M. C. CASIERO, J. D. ROBERTS and W. S. JOHNSON: Methylation of alcohols with diazomethane.

D. H. R. BARTON, P. DE MAYO, G. A. MORRISON and H. RAISTRICK: The constitutions of atrovenetin and of some related herqueinone derivatives.

T. URBAŃSKI: A study of the hydrogen bonds between the nitro group and the hydroxyl or amino groups in substituted nitroparaffins.

J. COMÍN and V. DEULOFEU: Studies on Argentine plants—XVII. The structure of fagarine II.

H. S. LANAI and W. N. LIPSCOMB: The structure of ψ-conhdrine.

A. J. BIRCH, H. SMITH and T. M. B. WILSON: The steric course of addition of some electrophiles to enolate anions derived from polycyclic systems.

W. VON E. DOERING and H. PRINZBACH: Mechanism of reaction of methylene with the carbon hydrogen bond: evidence for direct insertion.

H. J. E. LOWENTHAL: Selective reactions and modification of functional groups in steroid chemistry.

A. K. GANGULY and T. R. SESHADRI: A study of leucoanthocyanidins of plants—II. (+) Leucocyanidin from the gum of *Butea frondosa*.

GJ. STEFANOVIĆ, M. PAVIČIĆ-WOSS, LJ. LORENC, and M. LJ. MIHAILOVIĆ: Some applications of the Pfitzinger reaction. Condensation of isatin with diketons.

VOL. 4 1958

OL.
4
958